The epidemiology of cirrhosis and abnormal liver function in the general population of the UK

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Abstract

Background

Liver disease is a serious problem both in the UK and globally. While the incidence and mortality from several chronic diseases are decreasing, mortality from liver disease is increasing. As well as the medical sequelae for an individual with liver disease, in the UK the increase in chronic liver disease poses particular problems with respect to increasing hospital admissions, mortality and significant costs to the public both in terms of treatment and in loss of productivity. The increase in society of several risk factors for chronic liver disease, notably alcohol intake, obesity and type 2 diabetes, mean that these problems are likely to increase in the future.

Despite these apparent problems there are surprisingly few reliable sources of data on the occurrence of chronic liver disease (cirrhosis) in the general population of the UK and the rate and consequence of disease progression particularly among ambulatory patients. Nor are their robust estimates of the prevalence of abnormal liver function tests (which may represent undiagnosed liver disease) and their associations with mortality.

This thesis utilises two distinct datasets to examine separate areas of interest in the epidemiology of liver disease in the UK. The first three studies contained within this thesis are concerned with the epidemiology of cirrhosis in the general population of the UK. The second group of three studies focuses on the prevalence of elevated liver function tests in a population of older people in the UK, the demographic, clinical and lifestyle factors associated with such and the mortality following an elevated liver function test.

Objectives

1. To estimate the incidence and prevalence of cirrhosis in the population of the UK
2. To describe the mortality associated with cirrhosis compared with the general population and the disease progression of cirrhosis
3. To estimate the prevalence of elevated liver function tests among people aged 75 and over in the UK
4. To describe the association between elevated liver function test and demographic, lifestyle, clinical characteristics and mortality among people aged 75 and over.

Methods

To examine objectives 1 and 2 I utilised the General Practice Research Database (GPRD) constructing a population based cohort of 4537 subjects with cirrhosis and 44,403 age, sex and practice matched controls. I used Poisson regression to estimate incidence rate ratios and describe trends in alcoholic and non-alcohol-related cirrhosis. Using Cox regression within an historical matched cohort design I estimated the absolute excess mortality rates and hazard ratios for mortality in people with cirrhosis compared to the general population. I described the probability of progressing from one disease state to another.

To examine objectives 3 and 4 I accessed data from one arm of the Medical Research Council (MRC) Trial of Assessment and Management of Older People in the Community, a representative sample of community dwelling people aged 75 and over, totalling 15,308 participants. The prevalence of abnormal liver function was described as the proportion of study participants

with elevated aspartate transaminase, alkaline phosphatase or serum bilirubin. Associations between elevated liver function and demographic, lifestyle and clinical factors were examined using multivariable logistic regression. I determined the absolute mortality rates and hazard ratios for all-cause and cause-specific mortality using a Cox proportional hazards model.

Findings

Epidemiology of cirrhosis (GPRD)

These studies have shown an increasing trend in both the incidence and prevalence of cirrhosis in the UK with an estimated 45% increase in incidence of cirrhosis in the 10-year period studied. I estimate that 76 per 100,000 people were living with cirrhosis in 2001. Just over half of all cirrhosis was associated with alcoholism. Disease progression with cirrhosis among this mainly ambulatory population was rapid with a rate of decompensation in people with compensated disease of 5% per year and 1 in 10 dying in the first year following diagnosis. This figure increased to 25% of people dying within one year for those with decompensated disease. Mortality in subjects with compensated and decompensated cirrhosis was 93.4 and 178.0 per 1000 person years compared with only 19.2 per 1000 person years in the general control population. Following adjustment for age and sex people with compensated and decompensated disease were respectively 5 and 10 times more likely to die than the general population.

Epidemiology of abnormal liver function tests (MRC cohort)

Abnormalities in liver function were common with roughly 1 in 6 people aged 75 and over having at least one elevated liver enzyme, although most of these elevations were mild. A single elevated measurement of aspartate transaminase was associated with an increased consumption of alcohol and a

lower age in contrast with that of a single measurement of alkaline phosphatase which showed an association with higher age and lower alcohol consumption. An elevated bilirubin measurement was strongly associated with being male. Having a single elevated liver function test was associated with a modest increase in the hazard of death compared with people with normal liver function tests (adjusted hazard ratio for death 1.27 (95% CI[1.19, 1.36]). As well as an unsurprising increase in the hazard ratio for death from liver disease, elevated aspartate transaminase or alkaline phosphatase were both associated with modest increases in the hazard of death from cancer (adjusted hazard ratios of 1.56 (95%CI[1.21, 2.01]) and 1.61 (95%CI[1.39, 1.86]) respectively). Elevated alkaline phosphatase was additionally associated with increases in the hazard of death from respiratory disease (adjusted hazard ratio 1.58 (95%CI[1.32, 1.90])) and cardiovascular disease (adjusted hazard ratio 1.34 (95%CI[1.17, 1.55])).

Conclusions

From my work on the incidence and prevalence of cirrhosis I estimate that a minimum of 31,000 people in the UK are living with cirrhosis, a figure which is likely to rise given increasing trends in the incidence of cirrhosis described in this thesis. The significant mortality and disease progression associated with cirrhosis means that more needs to be done to combat both the incidence and progression of this disease both on an individual and population level.

Elevations in enzymes regarded as reflecting liver function are common in people aged 75 and over and in most people these abnormalities are less than 2x the upper limit of normal for the assays used. These elevations I observed are associated with both a modest increase in all-cause mortality and also with an increase in death due to specific causes. Rather than simply a marker of

liver function the investigation of people with elevated liver function tests, particularly those with severely elevated tests, may lead to the identification of potentially treatable conditions that underlie death.

Contributions

The studies contained within this thesis are based on existing data from two databases – the GPRD and "MRC Elderly".

GPRD studies

Joe West had the initial ideas, wrote the grant that funded my salary and obtained the initial extract of all liver disease data. I subsequently extracted data on patients with cirrhosis, performed all of the data management and analysis in the studies included in this thesis. I also conceived the idea to examine the progression of cirrhosis (Chapter 5). Masoud Solaymani-Dodaran provided an introduction to the data format of the GPRD. Joe West, Tim Card and Masoud Solaymani-Dodaran advised on data management, analysis and interpretation of the results. Guruprasad Aithal additionally provided advice on the clinical relevance of the results. Tim Card provided code lists used for the generation of the Charlson index.

"MRC Elderly" studies

Joe West had the initial idea for these studies. I performed the majority of the data management and all of the data analysis myself. I received help from Richard Atkins of the London School of Hygiene and Tropical Medicine in the preparation of cause of death data. Joe West and Astrid Fletcher advised on data management, analysis and interpretation of the results. Guruprasad Aithal additionally provided advice on the clinical relevance of the results.

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Joe West, my PhD adviser, boss, Harry-wannabe and, above all, dear friend. I would not have achieved this without your continued support, guidance, knowledge, shared love of Haribo, occasional whip-cracking and long-term friendship. I look forward to another 9+ years of epidemiology and world-domination planning. Thank you. You're (the) boss.

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Abbreviations used

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BASL	British Association for the Studies of the Liver
BMI	Body mass index
BSG	British Society of Gastroenterology
CI	Confidence interval
CMO	Chief Medical Officer
CTP	Child-Turcotte-Pug
DALY	Disability adjusted life-year
GGT	Gamma-glutamyl transpeptidase
GP	General Practitioner
GPRD	General Practice Research Database
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HES	Hospital Episodes Statistics
HR	Hazard Ratio
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	Internationalized Normal Ratio
LFT	Liver function test
MELD	Model for End-Stage Liver Disease
MHRA	Medicines & Healthcare products Regulatory Agency
MRC	Medical Research Council
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NHSCR	NHS Central Registry
ONS	Office for National Statistics
OR	Odds Ratio
OXMIS	Oxford Medical Information System
SMR	Standardised Mortality Ratio
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UTS	"up-to-standard"
VAMP	Value Added Medical Products
WHO	World Health Organization
WHR	Waist:hip ratio
YLD	Years lost with a disability

1. Introduction

This thesis utilises two distinct datasets to examine separate areas of interest in the epidemiology of liver disease in the UK. The first three studies contained within this thesis concentrate on the incidence and prevalence of cirrhosis, an examination of the mortality of people with diagnosed cirrhosis compared with those people in the general population and the progression of this disease. The second group of three studies focuses on the prevalence of elevated liver function tests in a population of older people in the UK, the demographic, clinical and lifestyle factors associated with such and the mortality following an elevated liver function test.

To contextualise these studies this introduction provides a brief consideration of some benefits and pitfalls in the methods of measurement of disease burden and gives an overview of the current burden of liver disease, globally and in the UK. I also describe what is presently known and unknown about the epidemiology of cirrhosis and that of elevated liver function tests in the elderly. Finally, a summary of the content of the subsequent chapters in this thesis is provided.

1.1. Measuring the burden of disease

The burden of disease, or the burden of a specific disease, can encompass a wide range of measures. These include

- the frequency of disease,
- the mortality from disease (and consequent years of life lost),
- the morbidity associated with disease, and
- aspects of societal burden such as the financial and service requirements associated with disease.

This section discusses briefly some relevant issues in measuring the burden of disease particularly with respect to chronic liver disease.

1.1.1. Measuring the frequency of disease

In its crudest form measuring the frequency of a specific disease can be considered as simply counting the number of people with that disease. Though this may appear, at first consideration, a very easy task it is in fact anything but for the vast majority of diseases.

The two principal ways of considering the frequency of disease in a population are the incidence rate and the prevalence of disease. The incidence rate refers to the identification of new cases of a disease within a determined population over a specified period of time. Prevalence is concerned with the total number of people within a given population who are presently living with the disease of interest. Incidence and prevalence are intrinsically linked with prevalence being a function of incidence and survival time consequent to the acquisition of disease in closed populations. In open populations the prevalence of disease may additionally be affected by migration.

Central to determining either incidence or prevalence are a precise definition of the disease of interest, knowledge of the total population at risk of the disease as well as the means with which to identify people with that disease.

1.1.1.1. The definition of a disease

Several methods may be employed which in isolation or combination lead to the diagnosis of a particular disease, or indeed the assertion that a particular disease is not present in an individual. These include the identification of histological changes in cell or tissue architecture, the presence or absence of clinical signs and symptoms, and the use of test results, such as laboratory diagnostic tests including blood serology. Frequently such signs, symptoms and tests in isolation are indicative of a disease but are not sufficient to warrant a formal diagnosis. As such the presence of signs and symptoms or positive tests can often be used as a measure of undiagnosed disease. In almost all circumstances to acquire a diagnosis a person must be seen by a health care professional of some sort.

1.1.1.2. Defining the population at risk

If a person is to acquire a disease at some point in their life they must be at risk of it. It is self-evident that women are not at risk of testicular cancer and any calculation of the incidence or prevalence of testicular cancer would therefore include as its denominator only the total number of men in that population. Similarly, studies of occupational injuries would only include working people within the population at risk.

However, for most diseases it is not possible or practical to identify people who are specifically at risk of the disease. For example, in a disease which requires genetic susceptibility it would be very difficult to exclude from the denominator those people who are not genetically susceptible. Consequently

the vast majority of incidence and prevalence calculations assume that the whole population is at risk of the disease.

Should the population of interest be a geographically determined region then administrative sources of data such as vital statistics (based on birth and death registers) or census data may provide an accurate estimate of the total population 'at risk'. However, if cases of disease are being identified through specific means e.g. presentation at hospital with particular symptoms, then it may not be as clear what the total population at risk is (see section 1.1.1.3).

1.1.1.3. Identification of people with disease

In an ideal world it would be very easy to identify the exact moment of disease onset (or time zero). Particularly with chronic diseases this is far from the case as disease can frequently be present before the onset of any signs or symptoms that would warrant investigation by a health care professional. Frequently in epidemiological studies the identification of cases of disease is a pragmatic one where the date on which a subject acquires a diagnosis of a particular disease is considered the date of disease onset.

Identifying all people with a particular disease on a truly population-based level is fraught with problems particularly if the diagnosis of disease requires histological confirmation, as is the case with several chronic liver diseases. Clearly it would be impractical and indeed unethical to perform an invasive procedure with attendant risks e.g. liver biopsy on all members of the general population, including those who are otherwise in apparently good health. Frequently, epidemiological studies are therefore based on populations of 'health-seekers' i.e. people who have for some reason been seen at a hospital or at the community level by a health practitioner, be it for the investigation of particular symptoms, following referral, for a routine health check or for an admission following an acute event. Whilst these study populations may be

representative of the total population of interest there is often likely to be some selection bias in those who are able to seek care.

For all calculations of incidence and prevalence the ideal scenario is a truly population-based approach but this is seldom achieved. However, it may be possible to conduct specific studies on a representative sample of a population, determine clinical signs and symptoms or obtain biological samples for laboratory testing and analysis, and then to extrapolate the results seen from this study population to the general population.

1.1.2. Measuring the mortality and morbidity associated with disease

Ideally once a person has acquired a diagnosis of a particular disease that person would be followed up for life and details regarding morbidity and death associated with the progression of that disease would be recorded and available for analysis.

Concerning morbidity, all aspects of altered health consequent to the acquisition of a disease should be recorded. This would include altered physical health in terms of the clinical manifestation of disease as well as the potential psychological impact of living with a disease.

With respect to mortality it is important to know whether the death of that person is a direct result of the disease in question, whether the disease has been a contributing factor in the death or indeed whether the disease played no part in that individual's demise. It is of benefit to know both the absolute mortality rates and the mortality relative to the general population to understand the effect of that disease on mortality.

1.1.3. Measuring the financial and service requirements associated with disease

In addition to the measurement of morbidity itself it is often desirable to obtain knowledge of the interventions, prescriptions or therapies that are associated with the management of disease and its symptoms as well as the effects of a disease with respect to an individual's ability to go about their everyday life.

In a country like the UK, where the overwhelming majority of healthcare is delivered free at the point of access through the National Health Service (NHS), it is essential that there are adequate estimates of the frequency and cost of treatments associated with a disease. For these figures to be of any real use in terms of the planning of services there must also be accurate estimates of the frequency of disease within a population to enable sufficient resource (personnel, equipment, facilities, in short, money) to be devoted to the treatment of particular diseases. Knowledge of the likely trends in the frequency of a disease is also of paramount importance for future planning requirements.

In addition, knowledge of the potential loss of productivity of individuals with a specific disease allows the assessment of the economic loss associated with the acquisition of disease. Several specific measures can be calculated including disability adjusted life-years (DALYs) and years lived with a disability (YLD).

1.1.4. Data used to measure the burden of disease

In the vast majority of settings and for the vast majority of diseases there are not sufficiently robust data available regarding the progress of individuals with disease to enable comprehensive assessment of the burden of disease with respect to any of the areas highlighted above. Indeed for most diseases there

are not sufficient data available concerning the incidence of disease, let alone the follow-up of patients with disease.

Notable exceptions to this include the monitoring of particular infectious diseases, for example cases of anthrax or cholera are required, by law, to be reported in the UK, and in many countries cancer, where comprehensive cancer registries exist, many of which can be aggregated to look at supra-national trends.

For other diseases aside from conducting specific bespoke studies there are sources of data which are commonly used to describe some aspects of the burden of disease among particular populations. I will consider the role of vital statistics, such as birth and death registration data, administrative health care data and long-standing surveys.

1.1.4.1. Vital statistics

Many estimates of the burden of disease rely on the estimation of total population numbers gained from 'vital statistics' i.e. the number of births and deaths (and ideally figures reporting migration) within a particular population. In many countries where birth and death registration are required by law these numbers are readily obtainable at a national and often at a fairly fine local level. However, in many countries, particularly in the developing world, estimates of total population numbers are more difficult to obtain with any precision.

In addition to the recording of the simple fact and date of these events, in many countries the registration of a birth or death must be accompanied by several pieces of information. For example, in the UK at the time of registering a birth information concerning the sex and birth weight of the child and country of birth of the mother are also collected. When registering a

death in the UK, information regarding the date, place and cause of death, as well as other information such as the occupation of the deceased, is collected. These two data sources are able to be linked together allowing, for example, the examination of trends in infant mortality based on birth weight of child and country of birth of mother.

Used alone, information regarding the cause of death is often used as an estimate of the frequency of disease within a population. For diseases with very high 1-year mortality, such as oesophageal cancer, this is a fairly good way to obtain incidence figures, providing the recording of cause of death includes that particular disease. With chronic diseases such as many liver diseases which people can live with for a very long time this measure will likely lag behind true population estimates of the frequency of disease. Additionally, the recording of cause of death on a death certificate is driven by what an individual doctor believes to be of importance. Though a person may have a long-standing illness, this illness may not have been of direct relevance to the fact of death and hence would not be recorded on the death certificate, leading to underestimates of the true population burden of that disease. For diseases where there are potential stigma attached to the diagnosis, such as liver disease with an aetiology of alcoholism, omission of certain diagnoses on the death certificate may be common in order to alleviate the suffering of the family members registering the death, again leading to underestimates of the true population burden of that disease.

Notwithstanding these limitations the availability of vital statistics is an extremely useful and well-used tool in measuring key population statistics which are readily comparable across nations and time.

1.1.4.2. Administrative health care data

In the course of providing care and treatment to patients in health care settings a significant quantity of data is collected which can potentially be used for epidemiological research and in part to measure the burden of disease. In the UK there are sources of data from both primary and secondary care.

Many practices in the primary care setting contribute data collected as part of the standard delivery of care to bespoke research databases which then allow access to researchers to study particular questions. I have used data from one such database for studies contained within this thesis and discuss the relative merits of such data in detail in Chapter 2.

In secondary care much of the information collected at a hospital level in the UK is available as part of 'Hospital Episodes Statistics' (HES). Each time a patient is admitted to hospital a certain amount of information is collected including the date of admission, demographic information about the patient and diagnostic and procedural codes determined by those administering care. Data on these admissions are often used as estimators of the incidence of disease within the population. As a patient can be seen many times for a single disease unless only the first episode of care a patient receives is counted these figures will inflate estimates of incidence. However, these data remain extremely useful for measuring the burden with respect to the service requirements of a particular disease.

Data collection at a hospital level is not driven by a specific research question eliminating much of the selection bias that may be present in bespoke research studies but limiting data in terms of what is collected. Indeed there are reported issues with the reliability of the recording of diagnoses and

procedures. With respect to the measurement of disease progression and morbidity, differences in surveillance and follow-up will exist in different locations rendering data from individual sites less generalisable than data obtained from the national database, which additionally provides large numbers with which to conduct a study.

1.1.4.3. Surveys

As a substitute or adjunct to data available from administrative health care data the collection of data through repeated cross-sectional surveys can provide a very valuable resource for the measurement of disease burden within a population. One such example of this, which has been used to great effect, is the National Health and Nutrition Examination Survey (NHANES), which periodically samples the US population. This survey constitutes a nationally representative sample of approximately 5000 people in the US, collecting information regarding risk factors for disease such as obesity, alcohol consumption and environmental exposures, as well as the presence or absence of chronic conditions such as diabetes, cardiovascular disease and kidney disease. All participants additionally attend a physician-led appointment where blood samples and body measurements are taken.
A similar survey in the UK exists in the form of the Health Survey for England (HSE) though this is not as comprehensive or well utilised.
Although there are limitations in the usefulness of data gained from cross-sectional surveys, not least the inability to assess the temporal nature of exposure and disease, these surveys nonetheless provide substantial information for the description of the burden of disease in the populations covered and, assuming the sampling has been well carried out, these data can be broadly generalised to the whole population.

Data from other cohort studies with substantial follow-up have been made available to researchers including, in the UK, the 1970 British Cohort Study and the Millennium Cohort Study.

1.1.5. Limitations in the measurement of disease burden

Although significant quantities of data are collected either routinely or as part of repeated surveys they are either a) not always appropriate for use in measuring the disease burden within a population or b) under-used considering they are available.

In the UK the provision of health care is increasingly concentrated to specialist services with tertiary referral centres for the treatment of particular diseases. As such, the use of single-centre (or indeed multi-centre) studies is more limited now as these study populations are often no longer representative of the geographic area normally served by that hospital. Rather than rely on traditional 'gold-standard' epidemiology (prospectively identified cohorts with long follow-up) which necessitate a considerable length of time before results are available it is perhaps increasingly more appropriate to utilise aggregated databases that are often available at a national level.

Having briefly discussed how we commonly measure disease I will now describe the burden of liver disease globally and in the UK.

1.2. The global burden of liver disease

Liver disease covers a broad spectrum of diseases including acute and chronic liver diseases. The International Classification of Diseases (ICD-10) includes within the specific section for liver disease (K70-K77) alcoholic liver disease (K70), toxic liver disease (K71), hepatic failure (K72), chronic hepatitis (K73), fibrosis and cirrhosis of liver (K74), inflammatory liver diseases (K75) and other diseases of liver (K76 including fatty liver K76.0). In addition, viral hepatitis (B15-19) and neoplasms of the liver and intrahepatic bile ducts (C22) are classed as liver diseases.

Throughout the world liver disease accounts for a considerable proportion of death, hospital admission, cost and DALYs. The relative contribution of specific liver diseases to the total burden of liver disease varies across the globe. I will briefly consider the global burden of chronic liver disease, viral hepatitis and liver cancer.

1.2.1. Chronic liver disease

The availability of data on chronic liver diseases varies dependent on the research activities and relative importance of chronic liver disease in individual countries or regions. The vast majority of the available data is concerned principally with cirrhosis, which I consider separately in section 1.4.1.

1.2.2. Viral hepatitis

Hepatitis is a general term referring to the inflammation of the liver. There are many different strains of viral hepatitis, the most common globally being hepatitis B and hepatitis C.

1.2.2.1. Hepatitis B

Hepatitis B, caused by the hepatitis B virus (HBV) is believed to have infected 2 billion of the world's population.[1] Most adult patients will recover from the infection but approximately 5-10% of people will not clear the virus. The prevalence of hepatitis B varies considerably across the globe with chronic HBV infection endemic (defined as greater than 8% of the population being carriers) in some areas of south-east Asia, sub-Saharan Africa, the Amazon Basin, part of the Middle East, central Asian Republics and some countries in eastern Europe (see Figure 1-1). Areas of low endemicity (carriers represent less than 2% of the population) include North America, Western and Northern Europe, Australia and part of South America with the rest of the world being classed as intermediate endemicity (carriers representing between 2 and 8 % of the population).

The principle route of transmission depends on the level of endemicity in a country, with mother-to-child transmission the most frequent method in areas of higher endemicity. In areas of lower endemicity more common transmission routes include high-risk sexual activity, blood transfusion in countries without donor screening, needle sharing and sometimes, although relatively rarely, through exposure to blood products in health care settings.

An estimated 350 million people worldwide are carriers of the HBV, often asymptomatic but frequently developing into chronic hepatitis, cirrhosis and/or liver cancer.

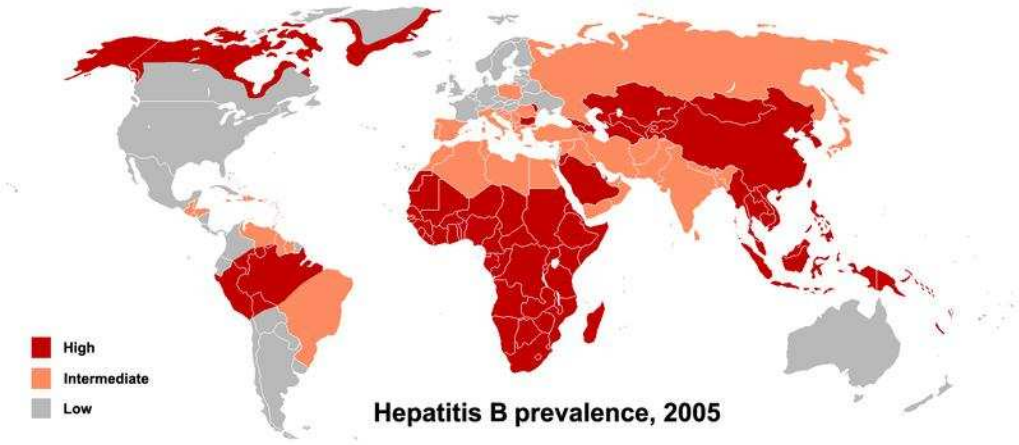


Figure 1-1 Global Hepatitis B prevalence, 2005.

1.2.2.2. Hepatitis C

Hepatitis C, caused by the hepatitis C virus (HCV), was identified in 1989, previously having been referred to as non-A non-B hepatitis. HCV is much less common than HBV with an estimated 3% of the world's population being infected.[2] HCV is more evenly distributed across the world than HBV but there remains substantial variation in the prevalence (see Figure 1-2).

The principle routes of transmission are through needle sharing, transfusion of unscreened blood products and, principally in areas of high endemicity, mother-to-child transmission.

Incidence of HCV is believed to be declining thanks to donor blood screening and needle-exchange programmes. As with HBV, most cases of HCV are asymptomatic so precise estimation of the prevalence is very difficult. HCV can progress to chronic hepatitis, leading to cirrhosis and liver failure in approximately 10-20%.[2 3 4]

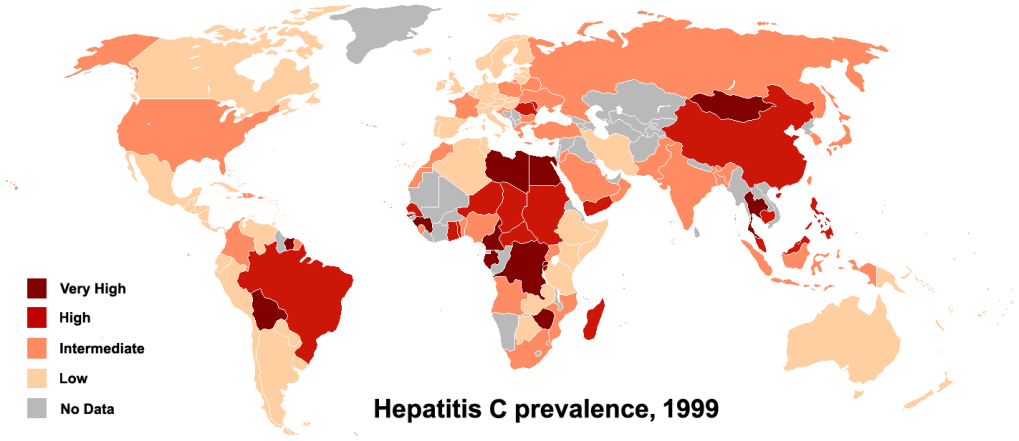


Figure 1-2 Global Hepatitis C prevalence, 1997.

1.2.3. Liver cancer

An estimated 632,000 cases of liver cancer occur every year across the globe.[5] Liver cancer ranks as the 6th most common cancer worldwide and the third most common cause of death from cancer worldwide.[6] The number of new cases of liver cancer is highest in the Western Pacific region (an estimated 386,000 in 2004) accounting for over three fifths of all cases whilst age-standardised incidence rates are highest for Eastern and South-East Asia and Middle and Eastern Africa (see Figure 1-3).

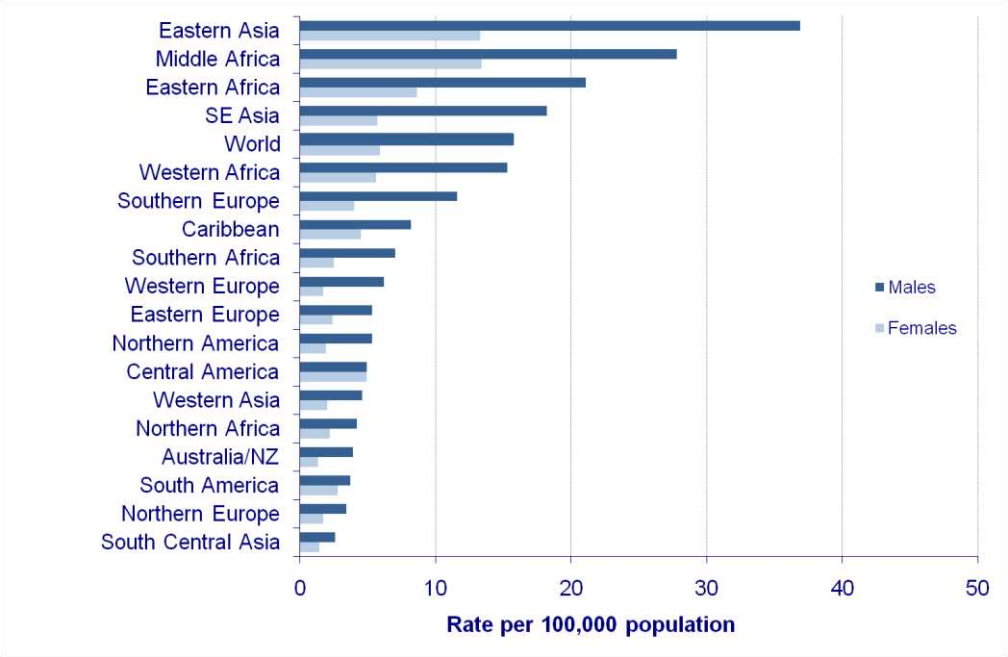


Figure 1-3 Age-standardised liver cancer incidence rates, by region and sex, 2002 estimates.
from Ferlay J. GLOBOCAN 2002. IARC CancerBase No.5, Version 2.0

1.3. Liver disease in the UK

The focus on liver disease in the UK is now principally concerned with chronic liver disease (including hepatocellular carcinoma), particularly chronic liver disease relating to increasing alcohol consumption, and, to a slightly lesser extent, HCV.

In the first decade of the 21st century there have been several documents published concerning the increasing problem of liver disease in the UK. Foremost was a chapter from the Annual Report of the Chief Medical Officer (CMO) for England in 2001 highlighting the problem of liver cirrhosis, particularly at younger ages.[7] Subsequent to this were four not insubstantial reports each concerning, at least in part, the burden of liver disease in the UK.[8 9 10 11]

The appointment of a National Clinical Director for Liver Disease in January 2010 would indicate that liver disease is considered a significant challenge to the NHS in the 21st Century.[12]

I will briefly consider the national burden of chronic liver disease, viral hepatitis, liver cancer and the demand for liver transplants.

1.3.1. Chronic liver disease

Estimates of the burden of chronic liver disease are largely based on mortality statistics and to a lesser extent on hospital admission statistics.

I will briefly summarise the five reports mentioned in section 1.3.
The report from the CMO highlighted a 3-fold increase in deaths from chronic liver disease (which it subsequently refers to as cirrhosis) over the period 1970-2000, with an 8-fold increase seen in men aged 35-44 and a 7-fold increase in women of the same age based on death certification data.[7] The most likely reason for this increase, according to this report, is the higher level of alcohol consumption in the UK over the same period. The report also briefly considers the role of viral hepatitis (particularly HCV) as an important cause of cirrhosis.

The second report, entitled 'The epidemiology and health care burden of chronic liver disease', commissioned by the British Liver Trust and the Foundation for Liver Research, published in December 2004 and included an examination of current knowledge of the epidemiology of several chronic liver diseases utilising data from mortality statistics, hospital episode statistics, cancer registry statistics and viral hepatitis notifications from the Health Protection Agency.[8] Analyses were limited to simple examination of time trends in mortality from particular diseases and admissions to hospital from these diseases and, in general, showed an increase in the burden of chronic liver disease. Again, considerable focus was given to the observed increase in alcohol consumption contemporaneously with an increase in mortality from liver disease.

In January 2006, a report prepared for the CMO by the Department of Health's Quality Strategy Team 'Liver Disease: a scoping study into the nature and burden of the disease' again provided a limited description of the burden of liver disease based on mortality statistics, data from the General Household Survey and the World Health Organization, as well as a brief summary of the current provision of liver services in the UK.[9] This report highlighted the lack of evidence about the incidence, nature and progression of liver disease in the United Kingdom.

The fourth report to consider was commissioned by the British Society of Gastroenterology (BSG) and published in February 2007.[10] 'Gastroenterology services in the UK. The burden of disease, and the organisation and delivery of services for gastrointestinal and liver disorders: a review of the evidence.' included a section on the incidence of liver diseases and mortality from liver disease based on a systematic review of the available literature and an examination of mortality statistics, with similar conclusions to the above reports, and a further consideration of the level of service provision in the UK.

The fifth report of note, 'A Time to Act: Improving liver health and outcomes in liver disease' published in 2009, prepared by the British Association for the Study of the Liver (BASL) and the BSG's Liver Section presented the national plan for liver services in the UK.[11] This report highlighted the potential preventability of much of the chronic liver disease affecting the UK, through alcohol harm reduction strategies, identification and reduction in transmission of HCV and through decreasing the prevalence of obesity.

In 2008 a paper summarised the trends in UK hospital admissions with a code for chronic liver disease and mortality rates based on death certification data

for all patients with a mention of liver disease.[13] Both hospital admissions and mortality from chronic liver disease were seen to increase over the period of 1989-2002.

There are, of course, many individual studies considering the burden of specific chronic liver diseases and the progression and mortality associated with such. However, a detailed examination of each of these diseases is beyond the scope of this thesis. A consideration of the epidemiology of cirrhosis is given in section 1.4.1.

1.3.2. Viral hepatitis

In the UK there is a low prevalence of active carriers of viral hepatitis with roughly 0.3% and 0.4% of the population infected with HBV and HCV respectively.[1 14]

However, there is considerable uncertainty surrounding the prevalence of these two viral hepatitides as so many patients whilst infected remain asymptomatic.

The reported increase in the prevalence of HBV is believed to be largely driven by immigration from areas of high endemicity.[11] The prevalence of HCV is reported to be lower in more recent birth cohorts, perhaps due to a decreased risk of infection in younger generations following the advent of blood screening and changes in injecting drug-users' habits.[15] Progression with HCV to cirrhosis in the UK is estimated at 12% (95% CI [6%, 22%]) over 20 years.[16]

1.3.3. Liver cancer

Figures from Cancer Research UK based on the cancer registrations of England, Scotland, Wales and Northern Ireland show an incidence of liver cancer in the UK in 2006 of 3193 new cases, accounting for just over 1% of all new cancers in the UK[17] placing liver cancer as the 18th most common cancer in the UK. Between the years 1975 and 2006 the age-standardised incidence rates of liver cancer in Great Britain have increased nearly 3-fold, from 1.4 to 3.9 per 100,000 person years.[17]

1.3.4. Liver transplant

Figures from the UK NHS Blood and Transplant Authority show 607 liver transplants in 2008/09 with a further 338 on the active transplant list at 31 March 2009.[18] For all patients on the transplant list, the most common reason for a liver transplant in the UK is cirrhosis (49% of all transplant patients) with metabolic and hereditary chronic liver diseases accounting for the majority of the remainder.(Personal Communication, UK NHS Blood and Transplant Authority, March 2010)

1.4. Rationale behind the studies in this thesis

1.4.1. Cirrhosis

What is cirrhosis?

Cirrhosis is a chronic liver disease defined anatomically as a diffuse process with fibrosis and nodule formation.[19] Its causes are myriad and it is considered the end point of most chronic liver diseases. Principle aetiologies are viral hepatitis, alcohol, autoimmune disorders such as autoimmune hepatitis and primary biliary cirrhosis, and metabolic disorders including haemochromatosis and Wilson's disease. Recent studies have suggested the progression of non-alcoholic fatty liver disease (NAFLD) to steatohepatitis, fibrosis and cirrhosis.[20] Frequently the aetiology of cirrhosis is unknown with such cases being commonly referred to as 'cryptogenic' cirrhosis. The aetiology of cirrhosis differs across the world, with alcohol representing a more common cause of cirrhosis in much of the Western world.

Diagnosis of cirrhosis

The diagnosis of cirrhosis is often based on a combination of clinical, ultrasound, biochemical and histological findings but liver biopsy is still considered the 'gold-standard' for the diagnosis of cirrhosis.[21] A liver biopsy carries with it some procedural risks, including bleeding, considerable discomfort for the patient and even a small risk of death,[22 23] so several other non-invasive methods for diagnosis are being more commonly employed and evaluated. These include transient elastography (Fibroscan), magnetic resonance elastography and combinations of ultrasound CT and MRI.[24 25]

Disease progression and treatment

Cirrhosis in the absence of complications is referred to as compensated cirrhosis but following the appearance of ascites, oesophageal variceal bleeding, encephalopathy or jaundice is considered to be decompensated. Cirrhosis has until recently been considered irreversible, but this concept is no longer absolute as regression of fibrosis can be seen and 'reversal' of cirrhosis has been reported.[26 27 28 29 30 31] The principle aim for therapies in patients with cirrhosis is to slow the rate of progression which would lead eventually to liver failure or death. Treatments are few and are mostly focussed on the removal of the aetiologic agent(s), the suppression of hepatic inflammation, inhibition of hepatic stellate cell activation and then therapeutic strategies for the common sequelae of cirrhosis including the early detection of hepatocellular failure, hepatocellular carcinoma, fluid retention, encephalopathy and prevention or treatment of oesophageal varices and oesophageal bleeding.

Global burden of cirrhosis

The global burden of cirrhosis of the liver is significant, accounting for an estimated 800,000 deaths (1.3%) worldwide in 2004 according to the World Health Organization (WHO) ranking it as the 18th highest cause of death.[5] In Europe, it is estimated to have contributed to 3.1 million DALYs (2.0% of total DALYs), ranking it as the 9th leading disease burden. Estimates of the years lived with a disability (YLD) for cirrhosis of the liver are as high as 3.79 million based on population estimates for 2000.[32]

UK burden of cirrhosis

In contrast to much of Western Europe, America and Australasia, where mortality from cirrhosis has remained constant or in decline, mortality from cirrhosis in the UK has tripled across the last few decades. [7 33] Although this increase is considerable the age-standardised mortality rates in England and Wales remain lower than those in most other countries studied, with the notable exceptions of Canada, Greece, and the Scandinavian countries (excepting Denmark).[33] Much of the increase in mortality from cirrhosis seen in the UK is attributed to the increase in alcohol consumption in the UK.[7 34 35] The commonly used definition for cirrhosis when examining mortality statistics includes codes for alcoholic liver disease (K70), chronic hepatitis (K73) as well as codes for fibrosis and cirrhosis of the liver (K74). In 2008, 1.3% of all deaths of people aged 25 years or over in England and Wales were attributed to these codes (K70, K73 and K74) according to death certification information.[36]

Despite the significant apparent burden of cirrhosis globally and the observation of an increasing trend in cirrhosis mortality in the UK there is little contemporary data surrounding the frequency of cirrhosis in the population of the UK, the mortality associated with a diagnosis of cirrhosis and the progression of the disease.

1.4.1.1. Incidence and prevalence of cirrhosis in the UK

Most reports examining the burden of cirrhosis in the UK concentrate on figures derived from death certificate information referring to a combination of chronic liver disease and cirrhosis (ICD-9 571 and ICD-10 K70, K73 and K74). As discussed above (section 1.1.4.1) there are significant limitations of mortality statistics to measure the burden of disease within a population, particularly a chronic disease such as cirrhosis. In addition, the inclusion of other chronic liver diseases which may not yet have developed into cirrhosis could lead to an overestimate in the burden of cirrhosis itself at a population level. These opposing potential misclassification biases mean estimates of incidence based on these mortality statistics are unlikely to be valid.

Despite the observed 3-fold rise in mortality from chronic liver disease the last studies to truly try to look at the incidence of cirrhosis in the population of the UK were reported nearly 30 years ago.[37 38]

The study by Saunders et al reported in 1981 presented a summary of data collected over 18 years in the 1960s and 1970s concerning patients aged 15 years and over identified to have cirrhosis from a single hospital in west Birmingham and from Coroner's post-mortem reports.[37] The incidence of cirrhosis was reported as 10.3 per 100,000 population. Though probably representative of the population served by this hospital, these figures are not generalisable to the rest of the UK as the West Midlands region has a higher than average mortality from liver disease compared with the general population of the UK.[39] In addition, 11.3% of the subjects in this study were identified as 'incident' cases as a result of incidental findings at post-mortem examination.

Information provided by Hislop in the form of a letter to the British Medical Journal in 1981 reports an incidence of cirrhosis of 14.6 per 100,000 population over the period of 1975-9.[38] Unfortunately I could not find a full publication of these results and the methods of data collection are unclear leaving the validity of these results questionable.

A third study reporting the incidence of cirrhosis on the islands of Lewis and Harris off the north-west coast of Scotland reported an incidence of 5.5 per 100,000 population based on only 12 patients with confirmed cirrhosis between 1977 and 1982.[40]

These wide estimates of incidence, mostly based on data from over 30 years ago and studies with varied methodology, provide considerable uncertainty to the present burden of cirrhosis in the UK. With this absence of contemporary studies on the incidence of cirrhosis we also have little idea as to future trends in mortality and we are unable to project the level of service provision required for treatments associated with the progression of cirrhosis, including liver transplantation and oesophageal banding.

1.4.1.2. Mortality experience of patients with cirrhosis

Whilst there are several studies which report the number of people who die with a recording of cirrhosis on their death certificate and the trends in such data there is little information about the mortality experience of patients with cirrhosis. We also have little idea of the comparative mortality experience of people with cirrhosis with reference to the general population.

The most recent estimate of survival in patients with cirrhosis in the UK comes from a regional study based on data from 1968-1999.[41] This study considered all patients in the Oxford Regional Health Authority who were admitted to hospital for any chronic liver disease (ICD-10 codes K70, K73, K74 and K76; ICD-9 and ICD-8 code 571) comprising 8192 patients across the whole period. The standardised mortality ratio (SMR), compared to mortality in the Oxford regional population, was 16.3 in the first year. The inclusion of only hospitalised patients will likely lead to an overestimate in the SMR as these patients requiring hospital admission are likely to be patients with more severe disease. As discussed above the inclusion of patients with other chronic liver diseases, not just specifically cirrhosis, may introduce some error into the estimates of mortality, though without knowledge of the relative mortality experience of patients with different liver diseases it is not possible to know in which direction this may change the point estimate of mortality. Additionally, it has been shown that the use of population death rates for comparators in mortality studies leads to an overestimate in the mortality risk suggesting an internal comparison group would be more appropriate.[42]

Other estimates of mortality in patients with cirrhosis in the UK come from much older studies. In the same study examining incidence Saunders et al

report the 5-year survival of patients with alcoholic cirrhosis, 36%, and non-alcohol related cirrhosis, 14%.[37] An earlier study, also from Birmingham, covering patients with cirrhosis in a single hospital between 1959-64 reports similarly low 5-year survival figures of 14.4% after first admission to hospital, again with patients with alcoholic cirrhosis having a better prognosis (5-year survival of 20% compared with 5.1% for patients with cryptogenic cirrhosis).[43]

There have been varying estimates in the mortality associated with a diagnosis of cirrhosis provided from other countries within Europe and the USA, all of which were based on hospitalised patients.

Perhaps the most commonly referenced figures in the literature looking at the mortality experience of patients with cirrhosis are those based on 1155 consecutive patients admitted to a single hospital in Sicily during the 1970s and 1980s which reported 6-year survival of 54% and 21% in patients with compensated and decompensated cirrhosis respectively.[44]

In Denmark between 1995 and 2006 a hospital cohort of 14,976 patients with cirrhosis described a 1-year survival of 65.5% and 5-year survival of 37.5%.[45] This study was not able to categorise patients into severity of disease and additionally did not report the hazard ratios for mortality compared with their matched control cohort. Previously these same authors had reported SMRs for patients hospitalized with cirrhosis compared with the general population of 32.3 for the first year following diagnosis and 5.7 thereafter.[46]

Two papers considering the experience of patients from the 1950s and 1960s report survival varying from less than 50% in the first year following diagnosis in Malmo, Sweden[47], to 60% in Brisbane, Australia.[48] Neither of these studies reported comparisons with a general population cohort.

Thus, most of our knowledge on the mortality experience of people with cirrhosis is from a few highly selected populations which may not be broadly representative of the whole population of people with cirrhosis, particularly with the absence of ambulatory patients. Previous studies have also been unable to take into account comorbid conditions and the aetiology and severity of cirrhosis itself. Indeed in a recent health technology assessment (HTA) systematic review it was claimed that existing data suggest that there is no excess mortality in those patients with compensated disease compared with the general population for the purposes of the cost-effectiveness analysis carried out.[49] Differences in the aetiology of cirrhosis in different countries may also render these estimates of mortality inappropriate for a UK cohort of patients with cirrhosis. There is clearly a need for contemporary estimates of the mortality experience of patients with cirrhosis within the UK, compared with a valid comparison cohort from the general population.

1.4.1.3. Progression with cirrhosis

Knowledge of the progression of disease is of natural interest to both physicians and patients alike wishing to understand the likely risks of subsequent morbidity and mortality associated with a diagnosis of cirrhosis. At an individual level and near the end stage of liver disease there are scoring systems commonly used to rank patients in order of risk of death and to enable identification of patients suitable for transplantation.

Two commonly used prognostic models in liver disease are the Child-Turcotte-Pugh (CTP) classification[50] and the Model for End-Stage Liver Disease (MELD) score.[51] The CTP score is a combination of five clinical measures of liver disease, each graded 1, 2 or 3. These are total bilirubin, serum albumin, internationalized normal ratio (INR), presence and severity of ascites and the presence and severity of hepatic encephalopathy. Limitations of the CTP score have led to the increasing use of the MELD score, a calculation combining serum bilirubin, serum creatinine and INR measurements using the following formula:

MELD = 3.78 [ln serum bilirubin (mg/dL)] + 11.2 [ln INR] + 9.57 [ln serum creatinine (mg/dL)] +6.43

Several modifications have been suggested to improve the measurements of current MELD components and the incorporation of other measurements, including coagulopathy, renal dysfunction and serum sodium, have also been suggested to improve the accuracy of the score's ability to predict survival.[52] The development of these scores primarily as a tool for identifying patients suitable for transplant may also mean that their utility as a score for cirrhosis itself may not be as valid as individual prognostic markers.[53] Some studies have examined prognostic factors specifically in cirrhosis using complex

regression models including 46 and 174 variables,[54 55] while there is a wide literature base of studies examining one or more individual prognostic factors. Whilst these scores are undoubtedly useful to clinicians in assessing the survival probability of an individual patient the complicated nature of the calculation and component parts may not be as readily comprehensible to patients themselves. As such, it is useful to have some knowledge of the progression of cirrhosis based on clinical symptoms which are easily understood by patients and clinicians alike and which do not necessitate laboratory tests.

Current knowledge of the progression of cirrhosis as a whole based on stage of disease is limited to a single centre study in Sicily, Italy from 1970s-80s,[55] and a recent study of hospitalised patients with alcoholic cirrhosis in Denmark.[56] Other studies have considered the prognosis of patients with cirrhosis once they have acquired certain symptoms such as oesophageal varices,[57] or variceal bleeding.[58 59 60] Whilst the more recent of these studies may provide useful information on the likely progression for patients with a diagnosis of cirrhosis they were all based on hospitalised patients only, some in populations with quite different risk factor prevalences to the UK, and were not able to examine the progression of disease based on severity and aetiology.

Understanding the contemporary disease progression in people with cirrhosis is key to determining the prognosis, health needs and burden of disease consequent upon having this serious condition.

1.4.2. Liver function tests

Several markers of liver function are included as part of standard laboratory blood tests which in the UK are frequently requested both in primary and secondary care. Standard blood tests which may be bracketed under the nomenclature of 'liver function tests' (LFTs) include serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, prothrombin time (INR) and gamma-glutamyl transpeptidase (GGT). None of these are truly specific in the measurement of liver function and as such the label of 'liver function test' is perhaps a little misleading. Nonetheless, these tests are useful on the diagnostic pathway and also as a prognostic tool. Additional tests that may be ordered on suspicion of liver disease may include several measurement of immunogloblulins (IgG, IgA, IgM), antimitochondrial antibody (AMA, used in the diagnosis of primary biliary cirrhosis), antinuclear antibodies (ANA, used in the diagnosis of autoimmune hepatitis), alpha-1 antitrypsin (used in the diagnosis of alpha-1 antitrypsin deficiency), caeruloplasmin (used in the diagnosis of Wilson's disease) and viral marker tests e.g. antibodies for the HBV and HCV.

I will focus the remainder of this section on a discussion of three commonly used 'liver function tests' namely aminotransferases (particularly AST), ALP and bilirubin.

<u>Aminotransferases (ALT and AST)</u>

ALT is a cytosolic enzyme present in the liver, and to a lesser extent in the heart and skeletal muscles. AST is a mitochondrial enzyme which is present in large quantities in the heart, skeletal muscle and kidney and also in the liver.

Variations in the serum prevalence of ALT and AST are indicative of the early stages of viral hepatitis, as well as other liver insults or injuries including alcohol abuse, autoimmune hepatitis, non-alcoholic steatohepatitis, haemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency. Non-hepatic causes of elevations in ALT or AST include coeliac disease, striated muscle disorders, some endocrine diseases (hyperthyroidism and Addison's disease) as well as glycogen storage diseases.[61] Often the ratio of the two enzymes is used in the diagnosis of alcoholic hepatitis and cirrhosis.

Alkaline phosphatase (ALP)

Alkaline phosphatase is an enzyme present in the liver and bile ducts. Elevations in ALP are common in cholestatic diseases (such as primary sclerosing cholangitis and primary biliary cirrhosis) but as ALP is also particularly concentrated in some other tissues (such as bones, placental tissue and in the kidneys) the specificity of ALP as a 'liver function test' is not very high. Elevations of ALP can occur in a wide variety of other diseases including Paget's disease and other bone disorders, with malignant tumours, in renal disease as well as natural elevations being seen during pregnancy. A simultaneous elevation in GGT would suggest a problem of liver origin.

Bilirubin

Bilirubin is a product of haemoglobin catabolism. An increase in serum bilirubin can be as a result of additional bilirubin production, decreased hepatic uptake or decreased conjugation (occurring within the liver). Elevations in unconjugated bilirubin can indicate haemolysis or familial abnormalities of bilirubin metabolism such as Gilbert's syndrome. Elevations in conjugated bilirubin are more indicative of congenital hyperbilirubinaemias such as Dubin-Johnson syndrome and Rotor's syndrome.[62]

Although these 'liver function tests' are performed frequently in both primary and secondary care the prevalence and consequences of these standard markers of liver disease have been ill-described in the UK making the interpretation of them difficult, particularly in the case of an isolated elevation in one of these tests.

A finding of an elevation of serum aminotransferase, ALP and / or bilirubin may be used as an indication of potential liver disease with subsequent follow-up or more invasive testing probable in such patients although specific guidance is not available in the UK.

One study in the UK examined the records of all patients from a single centre in the UK with an abnormal liver function based on a test requested from their GP.[63] Of 342 patients with an elevated LFT (a single measurement of ALT, ALP or GGT twice the upper limit of normal) just under half (157 patients (46%)) had initially not been considered to warrant further investigation. The authors invited these patients for subsequent tests which diagnosed liver disease in 97 (62%) of these patients. The remaining 195 patients from the original sample had their liver function test repeated with only 38% showing spontaneous resolution of the abnormal test results. Other studies from outside of the UK have reported high levels of liver disease in patients with persistently raised LFTs but who are otherwise asymptomatic.[64 65]

A report from the Department of Health's Quality Strategy Team (January 2006) recommended 'providing guidance to general practitioners on the use and interpretation of liver function tests'.[9] Current consensus opinion in the UK suggests that patients should be investigated only if abnormalities persist for between 3 and 6 months.

As the data I examined for chapters 7-9 only include measurements of AST, ALP and bilirubin for the remainder of this section when I refer to LFTs I am principally concerned with the measurement of serum AST, ALP and bilirubin only. As these data are also only concerned with people aged 75 and over I have tried to report studies specific to populations of older people. As this is a rapidly growing sector of the UK population who may be undergoing several tests as part of routine care for other conditions the quantification of the prevalence of abnormal LFTs, the association with demographic, lifestyle and clinical factors as well as subsequent mortality is of particular interest to clinicians who will be treating these patients.

1.4.2.1. Prevalence of elevated liver function tests

Information on the prevalence of elevated LFTs in the UK is surprisingly lacking. The only study I could find that specifically addressed the issue of prevalence of elevated LFTs in a UK population is the recent publication from McLernon and colleagues which examines LFTs in a population of adults of all ages from Scotland.[66] This study reports 21.7% of all study participants having at least one abnormal LFT with 7.0% having an elevated AST, 10.4% an elevated ALP and 7.1% an elevated bilirubin. Unfortunately this sample is unlikely to be representative of the general population as subjects were identified based on having already had a LFT recorded in primary care. As this is likely to include patients undergoing investigations for suspected liver disease these results cannot be widely generalised.

Other estimates of the prevalence of elevated LFTs come from outside of the UK and are often based on highly selected populations. Conflicting estimates from studies focussing on healthy employed workers place the range of elevated AST as low as 4.2% in Maryland, US[67] or as high as 21.8% in German construction workers[68] with a further study from the US placing the estimate of the prevalence of elevated AST at 14.9%.[69]

One study from America which identified patients who had had at least one healthcare encounter in the year 1995 estimated a prevalence of elevated AST of 13%. Again, as these patients are likely to include those who are sicker than the general population and therefore seeking health care this figure is probably an overestimate of the true population prevalence of elevated AST. Further studies from the USA using survey data from NHANES, a more representative sample of the population, have shown a much lower prevalence than that seen in the UK study, with 3.7% and 4.9% of

the population aged 20 or over having an elevated measurement of AST in 1988-1994 and 1999-2002 respectively.[70 71]

Fewer studies considered elevations in ALP and bilirubin. The study of a working population from Maryland, US reported a prevalence of elevated ALP of 5.9% and of elevated bilirubin of 8%.[67]

I did not identify any studies looking specifically at this problem in a population of older people.

Differences in the distribution of various risk factors, the prevalence of different liver diseases in these populations, the definitions of normal and abnormal tests as well as the methodological limitations in the selection of study populations mean that we are without a valid estimate of the prevalence of elevated LFTs in a UK population.

1.4.2.2. Associations with elevated liver function tests

Knowledge of the clinical, demographic and lifestyle factors that are associated with elevations in LFTs is crucial in the management of patients who may present with an elevated LFT.

It is important to know whether patients with elevated LFTs are a particular group of people (aside from whether they have liver disease) in order that we can potentially target the groups of people in whom further follow-up may be appropriate and also to aid in the understanding consequent to the identification of a person with elevated LFTs, particularly if there are specific comorbidities that are associated with elevations in LFT.

Many studies have looked at the association of certain 'risk factors' for elevated LFTs. Often these include the examination of elevated transaminases (either an elevation of ALT or AST) so it is not possible to determine what an elevation of one of these enzymes may be associated with. Markedly different associations have been shown, both in magnitude and indeed in some cases in the direction of the association. In addition, there is little consistency in the definition of abnormality employed in these myriad studies making comparisons and extrapolations to other populations difficult.

In the recent study from Scotland, an elevated measurement of ALP was associated with a statistically significant lower risk of several comorbidities (ischaemic heart disease, diabetes, respiratory disease and cancer) but with an increased risk of biliary disease.[66] However there were no statistically significant associations seen between transaminase elevations and these comorbidities studied. This is in contrast to the data from NHANES which

show an increased prevalence of type 2 diabetes and hypertension in patients with elevated transaminases as well as associations with younger ages, increasing BMI and being male[70] and data from Germany where elevated AST was associated with hypertension, ischaemic heart disease, hyperlipidaemia and higher BMI.[72] Of specific interest appears to be the association between abnormal LFTs and diabetes. Several papers have reported elevations of transaminases being associated with existing diabetes or the development of diabetes. [68 72 73 74]

There are again conflicts in the literature surrounding the association of elevated LFTs with alcohol consumption. Whilst three studies have reported an association between increasing alcohol intake and elevated transaminases,[68 71 75] another found no association between drinking 3 or more units per day and elevated LFTs.[69]

Differences in populations, definitions of abnormality and indeed the lack of consistency between these studies' findings leave a substantial gap in our knowledge of the associations between elevated LFTs and clinical, demographic and lifestyle factors. I was not able to find any papers that looked at the associations between elevated liver function tests and other characteristics specifically in a population of older people.

1.4.2.3. Mortality associated with liver function tests

Few studies have assessed the association between elevated LFTs and mortality in the general population as opposed to populations with known liver disease. Most of these studies have been performed in selected populations not broadly representative of the general population.

The only study to attempt to describe the relationship between elevated LFTs and mortality in the UK on a population-based level is the study by McLernon et al, described above.[66] This study reported statistically significant associations between elevated LFTs (transaminases, ALP and bilirubin) with increased all-cause mortality. Although moderate in absolute terms (for example, mildly elevated ALP (defined as elevated ALP between 1 and 2.5 times the upper limit of normal) was associated with a hazard ratio of 1.8 for all-cause mortality) the authors reported a higher risk of death with increasingly abnormal transaminases and ALP. The increased risk of death from liver disease specifically was markedly higher with hazard ratios of 3.8 and 5.4 for mildly elevated ALP and transaminases respectively.

A relatively recent study from the USA reported similar increased risks of death with elevated transaminases and a comparable 'dose-response' effect.[76] The study population was selected based on subjects who had had a healthcare encounter in a small geographically defined region of Minnesota and had at least 2 years of follow-up. Not all patients had their LFTs measured and as with the study in Scotland these populations are likely to include a significant proportion of subjects who were being actively investigated for liver disease meaning results cannot be widely generalised to the general population.

Two further studies from working populations in Germany and South Korea report markedly higher risks of death with elevated AST than the two studies described above.[68 75] Arndt and colleagues report a 3-fold increased relative risk of death from all causes in construction workers with an elevated AST, where Kim et al. report relative risks of mortality of 5.6 and above for increasing levels of abnormal AST. Indeed even within accepted normal limits subjects with a higher AST measurement than baseline (<20 IU/l) were seen to have an increased risk of death (relative risk 1.8 (95% CI[1.4, 2.4])).

I identified one study which looked specifically at the association between liver function and mortality in the elderly, which came from a small population of 70 year-olds in Jerusalem.[77] Categorising subjects as above or below the mean value of LFT, this study did not show a statistically significant association between elevated AST or ALP and all-cause mortality. However, they reported a higher mortality in patients with low ALT measurement in contrast to the above studies which considered transaminases together. No increased mortality was seen with elevated AST in a population of adults in the US.[73] The exclusion of subjects with excess alcohol consumption again introduces a significant selection bias into this population.

I did not identify any studies which specifically looked at the relationship between either AST, ALP or bilirubin with mortality from causes other than liver disease.

1.5. Thesis objectives

The overall objective of this thesis was to examine aspects regarding the epidemiology of cirrhosis and elevated liver function tests in the UK. Specifically, six linked studies were conducted and are outlined below.

Chapter 3 reports on the incidence and prevalence of cirrhosis in the UK.

Chapter 4 describes the mortality of people with cirrhosis in the UK compared with the general population.

Chapter 5 examines the progression of people with cirrhosis in the UK based on the identification of clinical symptoms.

Chapter 7 reports the prevalence of elevated liver function tests in a population of people aged 75 and over in the UK.

Chapter 8 describes the demographic, lifestyle and clinical factors associated with elevated liver function tests in this same population.

Chapter 9 examines the association of elevated liver function tests with all-cause and cause-specific mortality in people aged 75 and over in the UK.

In addition, **Chapter 2** describes the General Practice Research Database (GPRD) – the database used for the studies described within Chapters 3, 4 and 5 – and **Chapter 6** describes the "MRC Elderly" database – the database used for the studies described within Chapters 7, 8 and 9.

Finally, **Chapter 10** provides a summary of the main findings of this work and suggests directions for future research that have arisen from this thesis.

2. The General Practice Research Database

This chapter provides an overview of the General Practice Research Database (GPRD), its data format, its strengths and weaknesses particularly with reference to the studies in chapters 3 through 5 and details concerning the data extracted for use in the studies on cirrhosis contained within these three chapters. Additional study-specific information on the exact data used is detailed in the methods section of each individual chapter.

2.1. Introduction to the GPRD

The GPRD is a longitudinal database consisting of anonymous, computerised primary care records for over 13 million patients in the UK, including over 40 million person-years of data. Data included within this database are recorded through direct entry during face-to-face general practice appointments and also following information received from hospital care, including hospital letters and discharge summaries.

The GPRD was established in June 1987 as the VAMP (Value Added Medical Products) Research Databank as a commercial venture. In 1993 VAMP Ltd. was subsumed by Reuters, who donated the database to the Department of Health and renamed it as the GPRD. The GPRD is currently administered through the Medicines & Healthcare products Regulatory Agency (MHRA).

As part of the GPRD recording guidelines General Practitioners (GPs) are required to record certain data onto their desktop computers using Vision software which enables the database to be subsequently used for research purposes.[78] For all active patients in the practice the following data are required to be completed:

- Registration details, including date of birth, sex, date of registration with the individual practice and current registration status.
- Morbidity events, including events resulting in a hospitalisation or referral; events resulting in the prescription of a drug; and events requiring more than one consultation.
- Diagnoses, symptoms, procedures and investigations.
- Death details, including date of death and cause, if known.
- Pregnancy outcomes.
- Prescribing information.

Following entry into the GPRD a practice is required to submit at least 95% of this 'Research Information' to be considered "up-to-standard" (UTS).

2.2. Data format of the GPRD

The GPRD is a relational database which, at the time of data extraction for the work contained within this thesis (April 2002), was provided as four data files linked by a unique patient identifier (see Figure 2-1). The unique patient identifier in all files is a string variable combining the encrypted practice identification number and the encrypted patient identification number.

The four files comprise a patient data file, a medical data file, a therapy data file and a prevention data file.

The patient data file contains one line of data per patient per practice including the patient's date of birth, family identification number, sex, registration date with the practice, registration status, date of transfer out of the practice (if applicable) and the start and end dates pertaining to UTS data.

The medical data file contains information recorded each time the patient has an 'episode' including the event date, a code for the medical diagnosis, symptom or intervention utilising a modification of the Oxford Medical

Information System (OXMIS) classification and Read codes and the location of the consultation.

The therapy data file contains information recorded on any prescriptions that the patient might have received including the prescription date, the drug prescribed (coded using the Multilex drug code), and the quantity, dosage and duration of the prescription.

The prevention data file contains information recorded each time a patient has a test e.g. blood tests, and information recorded on other aspects of medical care including weight and height, vaccinations, smoking status and alcohol intake. The event date and the location are again recorded.

There can be several lines of data per patient in each of the medical, therapy and prevention files.

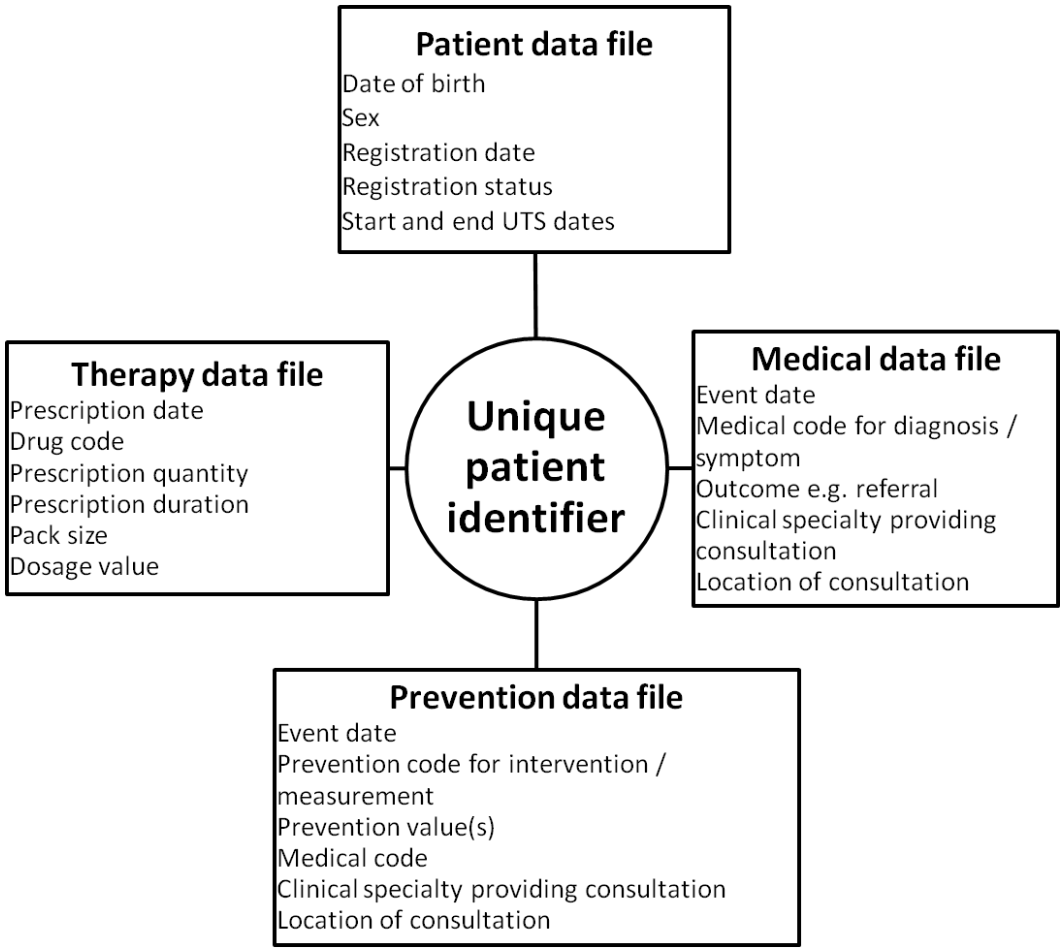


Figure 2-1 Structure of GPRD at time of data extraction

2.3. Strengths and weaknesses of the GPRD

The GPRD is an excellent resource for descriptive epidemiology and has been well utilised as such. However, as with any database there are limitations to its usefulness which should be considered. The relative merits and limitations of the GPRD, particularly with reference to studies of cirrhosis, are discussed below.

2.3.1. Size

The GPRD is a very large longitudinal primary care database making it a particularly attractive database for research into relatively uncommon conditions, including cirrhosis. Utilising such a large database as the GPRD will allow more precise estimates of the prevalence of cirrhosis and outcomes associated with this chronic disease than would previously have been afforded using smaller, clinically driven databases.

2.3.2. Representative

The practices included within the GPRD were initially self-selected but have subsequently been shown to be broadly representative of the general population of the UK in respect to estimates of levels of morbidity and mortality.[42 79] It would therefore seem reasonable to generalise results from the GPRD to the population of the UK as a whole with respect to the burden of a disease.

2.3.3. Prospectively collected

The majority of data within the GPRD are prospectively collected as part of the general course of medical care for each individual patient. Using the dates of the patient's entry into the practice and event dates it is possible to ascertain which data are prospectively collected and which are retrospectively collected. Hence there is much less opportunity for bias in the recording of individual diagnoses, symptoms or particularly exposures than might be present in smaller studies designed to answer a specific research question. Indeed there is no opportunity for bias in the reporting of primary care prescriptions as the prescription information contained within the database is generated electronically at the exact same time as the prescription itself is generated. However, as some of the data included in the GPRD are based on correspondence from secondary care it is possible that there is some misclassification in the recording of exact dates of events.

2.3.4. Contemporaneous

The data used in this thesis were extracted based on code lists for all patients with a record of one or more liver diseases between June 1987 and April 2002. For the assessment of the incidence of cirrhosis and subsequent mortality of those patients with cirrhosis, this represents a fairly contemporaneous data source for both those patients with cirrhosis and also the general population control cohort.

2.3.5. Validity

As well as ensuring that practices are contributing data that are considered "up-to-standard" the MHRA enables the independent validation of data by

researchers. Following the request for paper records, based on the unique patient identifier, GPs provide anonymised copies of the notes which can then be examined. Alternatively some GPs will be willing to complete questionnaires to validate particular points of interest on cases within the database. This cost of this service (at £100 upwards per validated subject) prohibits the validation of a large number of cases unless specific funding is obtained but does allow for the validation of a sample of cases. A recent systematic review identified 212 publications which included 357 validations of 183 different diagnoses and reported a median validation of 89% (range 24-100%).[80] A description of a validation for the diagnosis of cirrhosis is provided in Chapter 3.

2.3.6. Incomplete recording

As data in the GPRD are collected routinely as part of the normal course of care certain information that may be desirable for research purposes, particularly those regarding past exposures, may be missing. In addition, as the data collection is based on what is important in the opinion of the GP for the ongoing care of the individual patient it is likely that there is a bias to which information is collected. Looking at information regarding any chronic liver disease a particular example of this is in the recording of alcohol intake. It is highly likely that a GP will record the knowledge of a patient drinking heavily as this may affect health but conversely a patient may not be recorded as being teetotal unless they actually suffered from a condition that may be considered to be associated with alcohol use.

Another potential gap in the information recorded within the GPRD is that of medications that are either prescribed in secondary care or taken as over the counter medication without the need for a prescription.

2.3.7. Duration of follow-up

Although the GPRD is the largest longitudinal database of primary care data its size is limited in terms of the length of follow-up time that is contained on any individual patient with the maximum length of follow-up from index date in these data being 15 years. Indeed, as patients are free to change general practice whenever they wish, and there has been substantial turnover in participating practices during the lifetime of the GPRD, most subjects have considerably less follow-up than this. Though the power for the estimation of incidence within this database will be strong, the power for the follow-up of these incident cohorts is reduced due to the short length of individual person time.

2.3.8. Reproducibility

The GPRD is an ongoing database allowing for the application of the same methods again in order to assess trends over time.

2.4. Data used for chapters 3-5

2.4.1. Original data extracted for liver disease grant

Data were requested from the MHRA for all patients with a record of one or more liver diseases recorded between June 1987 and April 2002 based on several code lists. (See Appendix III-a Codes for liver disease)

For each case up to ten controls were requested, to be matched by gender, age (within 5 years) and practice. Each control had to be alive and contributing data to the GPRD on the date of the first occurrence of any liver disease (between June 1987 and April 2002) in their matched case's records. The control was not allowed to have a diagnosis of that same first recorded liver disease as their matched case throughout their GPRD record.

All data contained within the GPRD on both cases and controls (patient data files, medical data files, therapy data files, prevention data files and a linkage file to determine which controls were linked to which case) were provided in ASCII format. I subsequently imported these data into Stata version 9.2SE for all further manipulation and analyses.

2.4.2. Data manipulation for date variables

To ensure successful anonymisation of patients within the GPRD only the year of birth is included within the database. To enable suitable manipulation of these data the assumption of a date of birth of July 1 was imputed for all subjects. Though this will change the exact true length of follow-up for an individual patient the overall aggregated estimates of follow-up should not be biased unduly.

In addition the GPRD uses a redundant date of 1/1/1900. Any episodes with this date assigned were dropped from the data used for these studies.

2.4.3. Extraction of data on patients with cirrhosis

From this large dataset of all patients with any recorded liver disease and their matched controls I then extracted data for all patients with cirrhosis. Cirrhosis was defined using code lists for diagnostic and therapeutic codes for cirrhosis, portal hypertension and oesophageal varices (Table 2-1, Table 2-2, Table 2-3 respectively).

Codes for the specific disease of primary biliary cirrhosis were not included as this disease, although often a precursor to cirrhosis, is a distinct and different disease to cirrhosis itself.

Table 2-1 Medical codes for cirrhosis of the liver

Description	medcode
[X]OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER	Jyu7100
ALCOHOLIC CIRRHOSIS OF LIVER	J612.00
BACTERIAL PORTAL CIRRHOSIS	J615D00
BILIARY CIRRHOSIS	J616.00
BILIARY CIRRHOSIS NOS	J616z00
BILIARY CIRRHOSIS OF CHILDREN	J616200
CAPSULAR PORTAL CIRRHOSIS	J615600
CARDIAC PORTAL CIRRHOSIS	J615700
CARDITUBERCULOUS CIRRHOSIS	J615E00
CIRRHOSIS	5719CL
CIRRHOSIS - NON ALCOHOLIC	J615.00
CIRRHOSIS ALCOHOLIC	5710CA
CIRRHOSIS AND CHRONIC LIVER DISEASE	J61..00
CIRRHOSIS CARDIAC	5719CC
CIRRHOSIS OF LIVER NOS	J615z13
CIRRHOSIS PORTAL	5719CP
CONGESTIVE CIRRHOSIS	J615711
CRYPTOGENIC CIRRHOSIS OF LIVER	J615z12
DIFFUSE NODULAR CIRRHOSIS	J615300
FATTY PORTAL CIRRHOSIS	J615400
FLORID CIRRHOSIS	J612.11
GLYCOGENOSIS WITH HEPATIC CIRRHOSIS	C310400
HYPERTROPHIC PORTAL CIRRHOSIS	J615500
INFECTIOUS CIRRHOSIS NOS	J615H00
LAENNEC'S CIRRHOSIS	J612.12
LAENNEC'S CIRRHOSIS, NON-ALCOHOLIC	J615z14
LIVER CIRRHOSIS	5719HP
MACRONODULAR CIRRHOSIS	5719MA
MACRONODULAR CIRRHOSIS OF LIVER	J615z11
MICRONODULAR CIRRHOSIS	5710MC
MIXED PORTAL CIRRHOSIS	J615200
MULTILOBULAR PORTAL CIRRHOSIS	J615100
NON-ALCOHOLIC CIRRHOSIS NOS	J615z00
OESOPHAGEAL VARICES IN ALCOHOLIC CIRRHOSIS OF THE LIVER	G852300
OESOPHAGEAL VARICES IN CIRRHOSIS OF THE LIVER	G852200
PIGMENTARY CIRRHOSIS OF LIVER	C350012
PIGMENTARY PORTAL CIRRHOSIS	J615900
PIPE-STEM PORTAL CIRRHOSIS	J615A00
PORTAL CIRRHOSIS	J615.11
PORTAL CIRRHOSIS UNSPECIFIED	J615y00
POSTNECROTIC CIRRHOSIS OF LIVER	J615111
SECONDARY BILIARY CIRRHOSIS	J616100
SECONDARY BILIARY CIRRHOSIS (LIVER)	5719CB
SYPHILITIC PORTAL CIRRHOSIS	J615F00
TOXIC LIVER DISEASE WITH FIBROSIS AND CIRRHOSIS OF LIVER	J635600
TOXIC PORTAL CIRRHOSIS	J615B00
UNILOBULAR PORTAL CIRRHOSIS	J615000
XANTHOMATOUS PORTAL CIRRHOSIS	J615C00
ZOOPARASITIC PORTAL CIRRHOSIS	J615G00

Table 2-2 Medical codes for oesophageal varices

Description	medcode
[X]OESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE	Gyu9400
FIBREOPTIC ENDOSCOPIC BANDING OF OESOPHAGEAL VARICES	760C500
FIBREOPTIC ENDOSCOPIC INJECTION SCLEROTHERAPY OESOPH VARICES	760C300
FUND HOLDING OP OESOPHAGEAL VARICES	K298 FH
GASTRIC VARICES	G857.00
INJECTION OESOPHAGEAL VARICES	K2982
LIGATION OESOPHAGEAL VARICES	K2981
LOCAL LIGATION OF OESOPHAGEAL VARICES	7609300
OESOPHAGEAL VARICES	G85..11
OESOPHAGEAL VARICES IN DISEASES EC	G852.00
OESOPHAGEAL VARICES IN DISEASES EC NOS	G852z00
OESOPHAGEAL VARICES NOS	G858.00
OESOPHAGEAL VARICES WITH BLEEDING	G850.00
OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	G852000
OESOPHAGEAL VARICES WITHOUT BLEEDING	G851.00
OESOPHAGEAL VARICES WITHOUT BLEEDING IN DISEASES EC	G852100
OPEN INJECTION SCLEROTHERAPY TO OESOPHAGEAL VARICES	7609400
OPEN OPERATION ON OESOPHAGEAL VARICES NOS	7609z00
OPEN OPERATIONS ON OESOPHAGEAL VARICES	7609
OTHER SPECIFIED OPEN OPERATION ON OESOPHAGEAL VARICES	7609y00
RIGID OESOPHAGOSCOPIC BANDING OF OESOPHAGEAL VARICES	760F400
RIGID OESOPHAGOSCOPIC INJECTION SCLEROTHERAPY OESOPH VARICES	760F300
TANNER DEVASCULARISATION FOR BLEEDING VARICES	7609y11
VARIX OESOPHAGUS	4560

Table 2-3 Medical codes for portal hypertension

Description	medcode
PORTAL HYPERTENSION	5719PH
PORTAL HYPERTENSION	J623.00

2.4.4. Definitions used throughout

2.4.4.1. Death

Death was defined through a combination of medical codes denoting death within the medical data file (see Appendix III-b Codes for death), a recording of death in the prevention data file (code 16000000 denoting death) and the registration status of case within the patient data file (code 13 representing that the patient had died). As it is possible that recording of information on the registration status of a person could lag behind the recording of fact of death the earliest date of first recording of any of these codes was taken as the date of death of the patient.

2.4.4.2. Age

Age was defined both at index date and at date of diagnosis. Age was then categorised as necessary for individual studies (as described in the methods section for each chapter).

The studies in this thesis are concerned with adult liver disease. In order to examine only adult onset cirrhosis I excluded all cases with an age at diagnosis of less than 25 years to rule out the potential for including childhood diagnosed cirrhosis.

2.4.4.3. Alcohol

Within the GPRD it is possible to examine the alcohol consumption of an individual patient using information contained within the prevention data file on reported units of alcohol consumed in a week.

First of all I attempted to define alcohol consumption based on units of alcohol consumed as recorded in the prevention file. This had a high proportion of missing data rendering these data unusable in isolation for the purposes of identifying problem alcohol use. I then adopted a pragmatic approach of

classifying patients as non-drinkers, drinkers, alcoholics (including patients referred to alcohol cessation services) and patients with other problems associated with drinking based on combination of recorded medical codes relating to alcohol use and also unit consumption.(see Appendix III-c Codes for alcohol use)

3 Incidence and prevalence of cirrhosis in the UK

3.1 Introduction

This study aims to quantify the occurrence and prevalence of cirrhosis in the general population of the UK and describes the trends in liver cirrhosis incidence with respect to age, sex and presumed aetiology for the period 1992-2001.

3.2 Methods

3.2.1 Dataset used

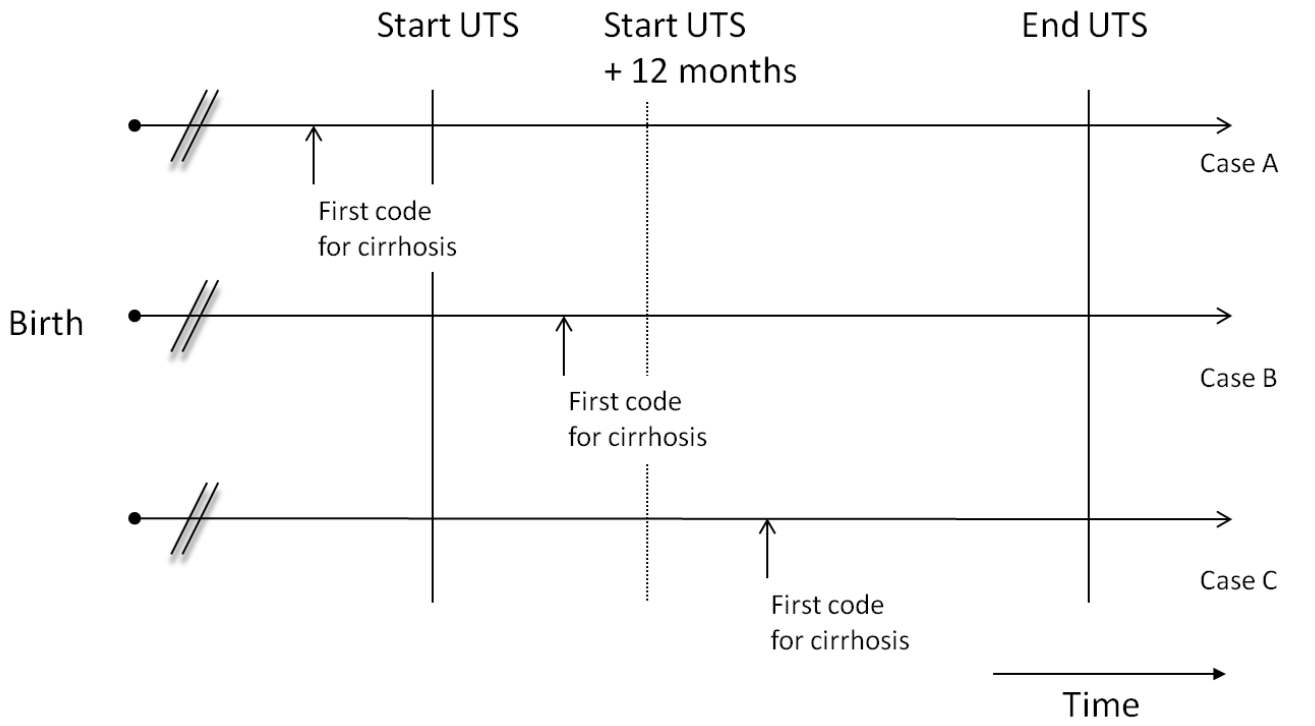
Data on all cases with cirrhosis (as described in section 2.4.3) were used in this analysis. Patients were assigned an UTS date as either the same UTS date as their general practice (for patients registered before the practice was considered "up-to-standard") or their date of registration (for patients registering after their general practice was considered "up-to-standard").

3.2.2 Additional definitions

3.2.2.1 Incident and prevalent cases

Patients were considered incident if the first recording of a diagnostic or therapeutic code for cirrhosis, oesophageal varices or portal hypertension occurred at least 12 months after the beginning of their UTS GPRD record. This method corrects for the potential for a prevalent case to be misclassified as an incident case following registration with a new practice and has previously been shown to more accurately reflect incidence rather than prevalence of other chronic diseases.[81] All patients with a first diagnosis of

cirrhosis before the beginning of their UTS GPRD record, or within the first 12 months following the start of their UTS record, were considered to be prevalent (see Figure 3-1).



Case A. First code for cirrhosis before Start UTS = prevalent
Case B. First code for cirrhosis within 12 months following Start UTS = prevalent
Case C. First code for cirrhosis after 12 months following Start UTS = incident

Figure 3-1 Timeline to represent selection of cases as prevalent or incident

3.2.2.2 Aetiology of cirrhosis

I examined 4 specific presumed aetiologies: alcoholic, viral hepatitis, autoimmune liver disease and metabolic liver disease. All aetiologies were ascribed using data from the whole GPRD record, not just before the diagnosis of cirrhosis to capture investigations into the aetiology that may have been instigated subsequent to the diagnosis.

For the purposes of aetiology analysis alcoholic cirrhosis was defined as any mention of alcoholism, alcohol abuse, addiction or dependence i.e. all those patients classified as 'alcoholic' in their medical files (see section 2.4.4.3). Viral hepatitis included all forms of known viral hepatitis (see Appendix III-d Codes for viral hepatitis). Autoimmune liver disease consisted of primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis (see Appendix III-e Codes for autoimmune liver disease). Metabolic liver disease consisted of haemochromatosis, Wilson's disease and alpha-1 antitrypsin deficiency (see Appendix III-f Codes for metabolic liver disease). All other patients were subsequently labelled as 'other unspecified causes of cirrhosis'. For the purposes of trend analysis, all cases not fulfilling the definition of alcoholic cirrhosis were grouped together as non-alcohol-related cirrhosis.

3.2.2.3 Age

Age at diagnosis was subsequently categorised into 10-year age bands from 25-34 to 85+ years.

3.2.3 Validation

In order to assess the accuracy of the recording of the diagnosis of cirrhosis paper records from the GPs were requested from a stratified, random sample of patients with a diagnostic or therapeutic code for cirrhosis. The patients' paper records were then examined by a consultant hepatologist (Guruprasad P Aithal). Information was gathered on whether there was any record of cirrhosis, whether the diagnosis had been made in primary or secondary care, whether this had been confirmed by biopsy and whether there was any record of the presumed aetiology of the cirrhosis.

3.2.4 Statistical analysis

3.2.4.1 Incidence

To calculate overall incidence I used the total number of new cases of cirrhosis i.e. those cases whose first record of cirrhosis was recorded 12 months after the start of the 'up-to-standard' period (see section 3.2.2.1) as the numerator and the total population of the GPRD aged 25 years and over as the denominator, by summing the mid-year population numbers for each valid year. I excluded data previous to 1992 owing to the small number of practices contributing data in these years. Data from 2002 were also excluded as there was not a full calendar year of data available. I initially calculated crude incidence rates and then stratified by year of diagnosis, age group and sex. I also examined the trend in incidence of alcoholic and non-alcohol-related cirrhosis. Poisson regression was used to model fully adjusted incidence rate ratios and estimate confidence intervals.

3.2.4.1.1 Alternative case definitions

To account for potential over- and under-ascertainment bias I performed two additional analyses. To minimise the potential over-ascertainment bias introduced by including cases with oesophageal varices and portal hypertension who may not actually have cirrhosis I calculated incidence based purely on those cases with a medical code for cirrhosis (see Table 2-1). This provided a minimal estimate of incidence.

To minimise the potential of missing cases with underlying cirrhosis but lacking a formal diagnosis I searched the GPRD for patients with recorded liver disease and a further recording of non-malignant ascites (see Table 5-1) and/or encephalopathy (see Appendix III-g Codes for encephalopathy). I examined the trend in incidence with and without these cases. This provided a maximal estimate of incidence.

3.2.4.2 Prevalence

I calculated three separate point estimates of prevalence using all cases who were still contributing data to GPRD at 1 July 1993, 1 July 1997 and 1 July 2001. The total GPRD population aged 25 years or older at each time point was used as the denominator.

3.2.4.3 Application of results to 2008 population

I applied the age- and sex-specific incidence and prevalence figures to the 2008 age- and sex-stratified population of the United Kingdom to estimate the number of people being newly diagnosed with cirrhosis in the UK and the number of people living with cirrhosis in the UK.[82]

3.3 Results

3.3.1 Study population

A total of 3,360 incident cases of cirrhosis aged 25 or over were identified between 1992 and 2001, 58% of whom were male. The median age at diagnosis was 56.3 years in men and 61.3 years in women ($p<0.001$). Thirteen per cent of cases had their first recording of cirrhosis concurrent with the recording of time of death following correspondence from secondary care services. Over half of patients (n=1690, 50.3%) had a recording of alcoholism at any point within their GP records (see Table 3-1). For 1591 cases (47.4%) alcohol was the only specified associated factor. Overall, just under two-fifths of cases had no specified aetiologies within their GP record (n=1328, 39.5%), a proportion which remained roughly constant across the study period.

Table 3-1 Presumed aetiology of incident cirrhosis cases

Presumed aetiology*	n (%) N=3360
Alcohol-related	**1690 (50.3)**
Alcohol-related only	1591 (47.4)
Alcohol-related and viral hepatitis	77 (1.7)
Alcohol-related and autoimmune disease	11 (0.3)
Alcohol-related and metabolic disease	10 (0.3)
Alcohol-related, viral hepatitis and metabolic disease	1 (<0.1)
Viral hepatitis	**181 (5.4)**
Viral hepatitis only	111 (3.3)
Viral hepatitis and alcohol-related	77 (1.7)
Viral hepatitis and autoimmune disease	5 (0.1)
Viral hepatitis, alcohol-related and metabolic disease	1 (<0.1)
Autoimmune disease	**237 (7.1)**
Autoimmune disease only	225 (6.7)
Autoimmune disease and alcohol-related	11 (0.3)
Autoimmune disease and viral hepatitis	5 (0.1)
Metabolic disease	**29 (0.9)**
Metabolic disease only	19 (0.6)
Metabolic disease and alcohol-related	10 (0.3)
Metabolic disease, alcohol-related and viral hepatitis	1 (<0.1)
Other, unspecified	**1328 (39.5)**

*NB As some combinations of presumed aetiologies are included more than once, numbers in the table do not add up to 3360

3.3.2 Incidence

Over the 10-year period crude incidence was 14.5 cases per 100 000 person years, increasing from 12.0 in 1992 to 17.0 cases per 100 000 person years in 2001 (see Table 3-2).

This increase fitted a continuous model with an average yearly incidence rate ratio of 1.04 (95%CI [1.03, 1.06]) adjusted for age and sex, corresponding to a 45% increase in incidence over the decade studied. Incidence was about 50% higher in men than women, 17.5 cases per 100 000 person years and 11.8 cases per 100 000 person years respectively (incidence rate ratio 1.52; 95% CI [1.42-1.63] adjusted for age and year of diagnosis) (see Figure 3-2). Figure 3-3 shows that the incidence of cirrhosis was higher in men than women for all age groups. The highest incidence for women occurred at age 65-74 years (22.7 per 100 000 person years). Incidence at all age groups from 45-84 years for men was higher than this maximum for women.

Table 3-2 Incidence of cirrhosis, 1992-2001

	Cases	P-years	Crude incidence rates [95% CI] per 100 000 p-years
Total	**3360**	**23 093 805**	**14.5 [14.1, 15.0]**
Sex			
Female	1406	11 934 462	11.8 [11.2, 12.4]
Male	1954	11 159 343	17.5 [16.8, 18.3]
Age (years)			
25-34	122	5 194 894	2.3 [2.0, 2.8]
35-44	461	4 776 754	9.7 [8.8, 10.6]
45-54	816	4 419 818	18.5 [17.2, 19.8]
55-64	790	3 362 078	23.5 [21.9, 25.2]
65-74	727	2 854 265	25.5 [23.7, 27.4]
75-84	386	1 828 533	21.1 [19.1, 23.3]
85+	58	657 463	8.8 [6.8, 11.4]
Year			
1992	339	2 813 552	12.0 [10.8, 13.4]
1993	337	2 771 663	12.2 [10.9, 13.5]
1994	378	2 674 596	14.1 [12.8, 15.6]
1995	339	2 655 872	12.8 [11.5, 14.2]
1996	352	2 411 170	14.6 [13.2, 16.2]
1997	357	2 253 388	15.8 [14.3, 17.6]
1998	355	2 157 349	16.5 [14.8, 18.3]
1999	340	2 036 987	16.7 [15.0, 18.6]
2000	319	1 883 106	16.9 [15.2, 18.9]
2001	244	1 436 120	17.0 [15.0, 19.3]

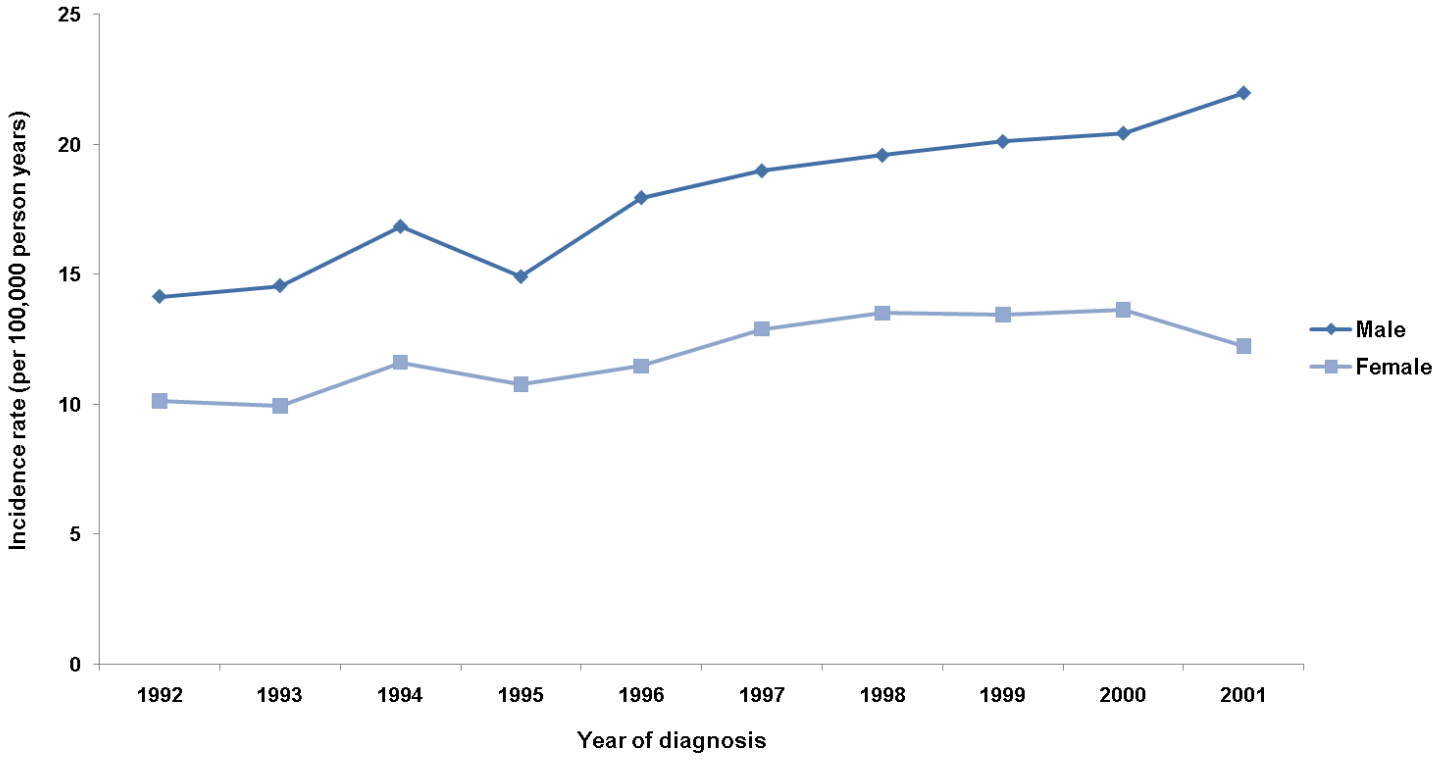


Figure 3-2 Incidence of cirrhosis (per 100,000 person years) by year and sex, UK, 1992-2001

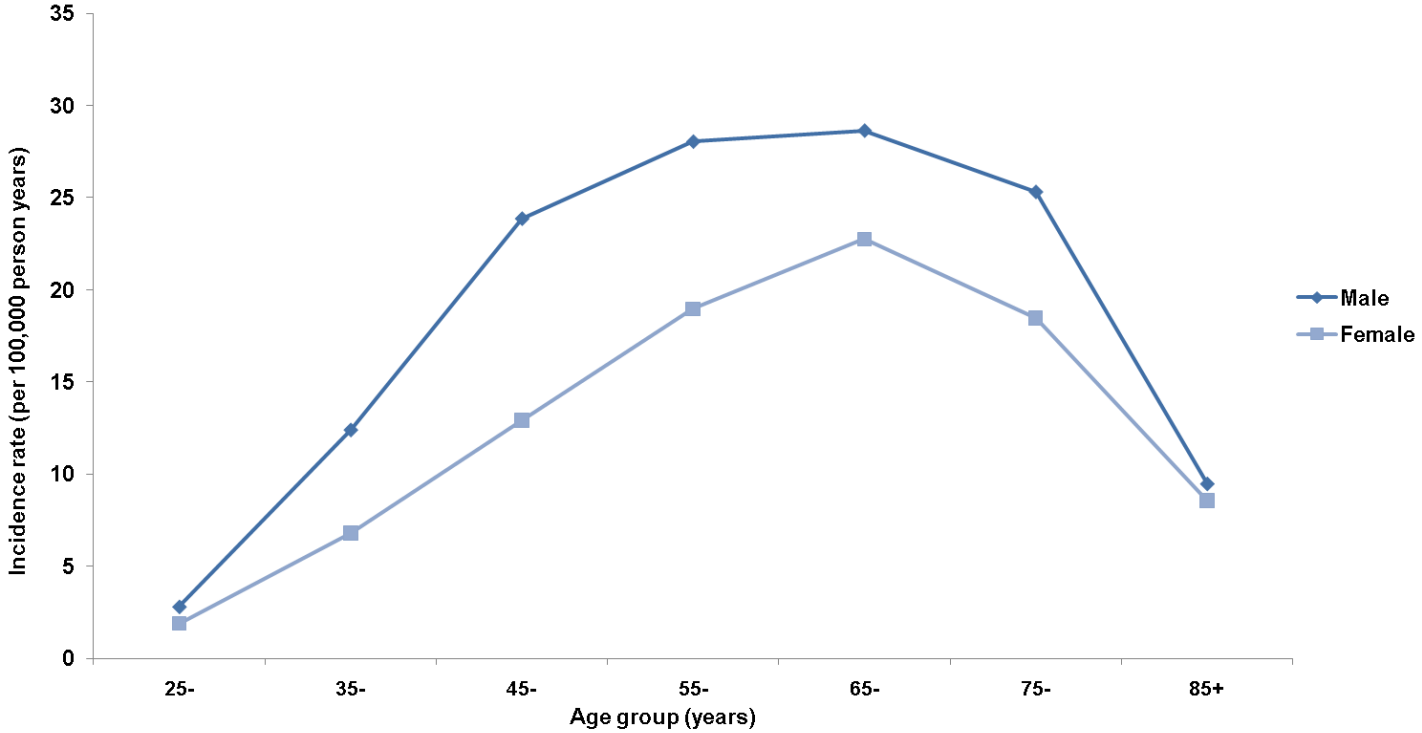


Figure 3-3 Incidence of cirrhosis by age group and sex, UK, 1992-2001

3.3.2.1 Alcoholic and non-alcohol-related cirrhosis

Within the study population just over half (50.3%) of people with a record of cirrhosis were defined as alcoholic cirrhosis, according to the criteria described above (see Table 3-1). An increase in the incidence of both alcoholic cirrhosis and non-alcohol-related cirrhosis was seen in men, 70% ($p<0.001$) and 30% ($p=0.017$) increase respectively across the 10-year period, and also in women, 28% ($p=0.068$) and 36% ($p=0.004$) increase respectively over the 10-year period (see Figure 3-4 and Figure 3-5).

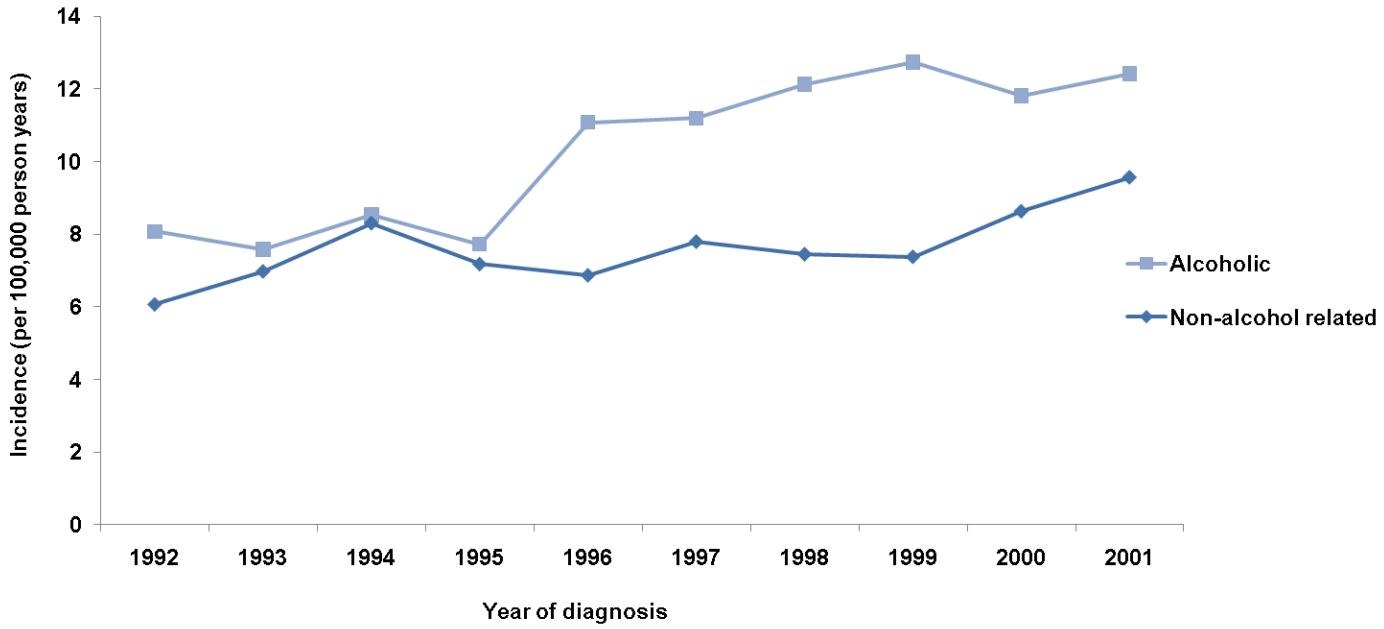


Figure 3-4 Incidence of alcoholic and non-alcohol-related cirrhosis in males, UK, 1992-2001

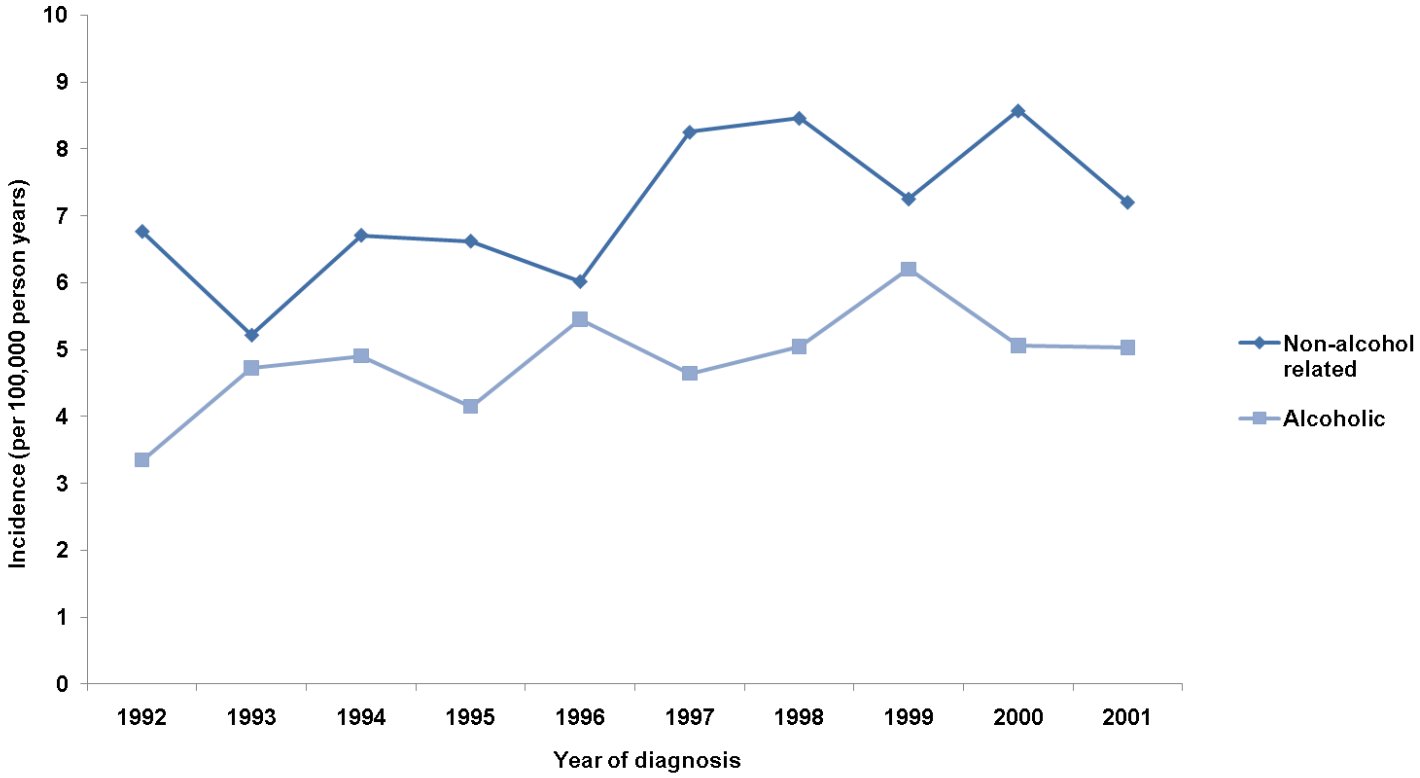


Figure 3-5 Incidence of alcoholic and non-alcohol related-cirrhosis in females, UK, 1992-2001

3.3.2.2 Incidence using alternative case definitions

Including only patients with a diagnosis of cirrhosis itself i.e. excluding those patients with a diagnosis of oesophageal varices and portal hypertension the overall crude incidence, 1992-2001, decreased by 15% from 14.5 to 12.4 per 100,000 person years (see Figure 3-6).

Using the extended definition of cirrhosis an additional 505 incident cases were included. The overall crude incidence, 1992-2001, when the additional patients with liver disease and non-malignant ascites or encephalopathy were included, increased by 15% from 14.55 to 16.74 per 100,000 person years (see Figure 3-6).

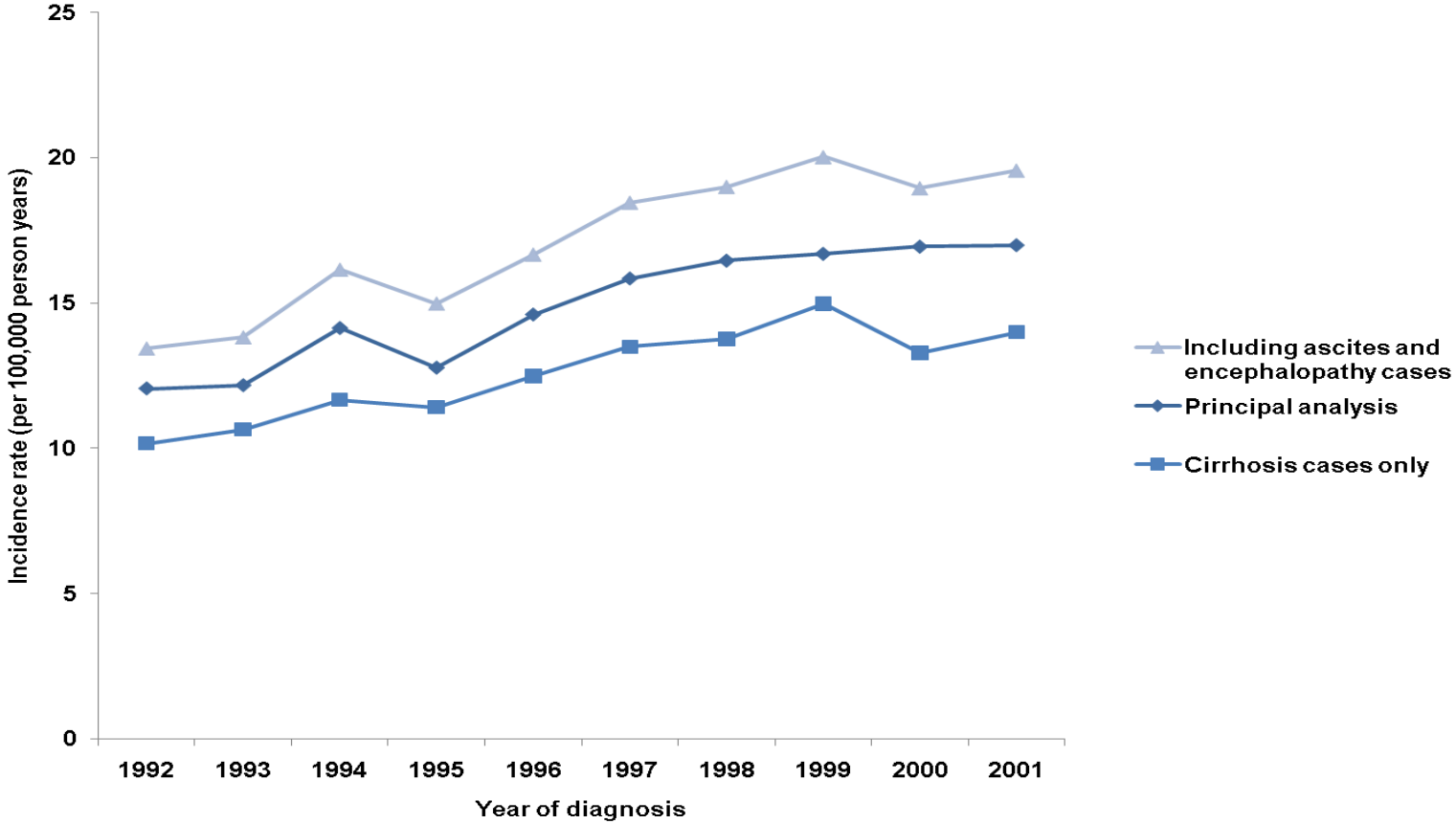


Figure 3-6 Incidence of cirrhosis using alternative case definitions

3.3.3 Prevalence

Using all cases contributing to the GPRD at three separate time points I observed an increase in the prevalence of cirrhosis between 1 July 1993 and 1 July 2001 from 45.4 to 76.3 per 100,000 population aged 25 years or over (see Table 3-3) representing a 68% increase in the prevalence of this disease over the period studied. Prevalence was higher in men than women at all three time points.

Table 3-3 Prevalence of cirrhosis

	Prevalence (per 100,000 population)			
	Females	Males	Total	Prevalence rate ratio *
1 July 1993	38.6	52.8	45.4	1
1 July 1997	58.2	74.8	66.2	1.46
1 July 2001	65.9	87.2	76.3	1.68

*compared with 1 July 1993

3.3.4 Validation

Responses were received for 49/59 patients whose notes were requested, a response rate of 83%. Of the responses received 13 sets of case notes were not available because either the patient had subsequently moved from the GP surgery (6), the patient had died (2) or the GP was unable to help (5). Of the 36 sets of case notes that could therefore be examined, 35 cases had chronic liver disease (97%, 95% confidence interval [85%, 99.9%]). A total of 27 patients (75%, 95% confidence interval [58%, 88%]) had evidence confirming cirrhosis, either biopsy proven cirrhosis, evidence of portal hypertension (with supportive evidence of liver disease as the cause of the portal hypertension) or clinical decompensation in the presence or absence of advanced changes seen at biopsy. Of the nine cases where cirrhosis could not be confirmed, all bar one had evidence of chronic liver disease - three cases of primary biliary cirrhosis, three cases of alcoholic liver disease and one each of Budd-Chiari and autoimmune hepatitis. The one case which could not be considered as chronic liver disease was a patient with alcoholic pancreatitis. All of these diagnoses occurred in secondary care.

3.4 Discussion

3.4.1 Key findings

This study has described a 45% increase in the incidence of cirrhosis in the UK in the decade between 1992 and 2001 and a 68% rise in the prevalence. Cirrhosis occurred more commonly and at younger ages in men than women. Nonetheless, a significant increase in incidence was seen for all age groups and for both sexes across the period under study. Incidence of both alcoholic and non-alcohol-related cirrhosis increased in males and in females during the period.

Applying the 2001 prevalence and incidence figures to the 2008 age- and sex-stratified population of the UK, I estimate that, over the age of 25, at least 31,000 people in the UK are currently living with cirrhosis and approximately 7100 people are being newly diagnosed with this disease each year. If I use the estimate from the wider definition of cirrhosis this figure increases to an estimated 8000 people being newly diagnosed with cirrhosis each year. These figures are still likely to be an underestimate of the burden of cirrhosis since they are based on diagnosed disease and do not take into account the possibility of a continuing increasing trend. This clearly represents a challenge for health care services and will have substantial implications for the future trends in mortality from this disease.

3.4.2 Strengths and limitations

This is the first UK-wide population-based study of the occurrence of cirrhosis. I have examined contemporary data from general practices representative of the UK collected over a period of 10 years. The collection of data within the GPRD is not driven by a specific research question and is hence not subject to

the same ascertainment biases as may be present in smaller, hospital-based series.

The biggest potential limitation of this study lies with the case definition, having included as cases all patients with any mention of cirrhosis, oesophageal varices or portal hypertension within the primary care records. Although it is possible that portal hypertension and oesophageal varices are manifestations of diseases other than cirrhosis it was decided to include these codes within the list for cirrhosis as these symptom are widely regarded as being representative of cirrhosis in developed countries. The validation exercise, which took the form of a case note review, showed that the majority (75%) of the sampled cases had an assertion of cirrhosis within the medical records. Of the remaining 25% of patients, 8/9 had a confirmed chronic liver disease with the potential to develop cirrhosis, although cirrhosis itself was not recorded in the notes available to us. All of the confirmed diagnoses examined in the case note review had been communicated to the GP directly from secondary care. It is reasonable to suppose that this is a sufficiently robust definition to accurately capture cases of cirrhosis recorded in the GPRD and in such a way which is easily replicated allowing valid examination of trends over time. Although I may have inadvertently included as cases a few patients who did not have cirrhosis it is more likely that I am missing cases of cirrhosis where diagnosis was unconfirmed and/or not fed back from secondary care into the primary care records. This finding of an increase in incidence is unlikely to be due to increased ascertainment through diagnostic procedures as UK Hospital Episode Statistics report a decrease in the number of diagnostic fibre optic examinations of the upper gastrointestinal tract (-4%) in the period 1995/6 to 2004/5.[83]

While it was not possible to assign a presumed aetiology to 39% of cases from the available data this is similar to the largest previous study of cirrhosis with 35% being labelled as cryptogenic cirrhosis.[37] I have considered all patients with specific recording of alcoholism as having alcoholic cirrhosis. Owing to the known limitations of recording and referral for alcohol-related problems by GPs within this dataset,[84] it is likely that I have underestimated the number of patients with alcoholic cirrhosis. Although it is possible in a patient with recorded alcohol problems that alcohol intake itself was not the underlying cause of the cirrhosis, it is more likely that the true proportion of alcoholic cirrhosis is greater than the 50% seen in these data.

3.4.3 Comparison with previously published work

The largest study, prior to this study, looking at the incidence of cirrhosis in the UK was a summary of data collected over 18 years in the 1960s and 1970s.[37] This previous study, which comprised 512 people identified to have cirrhosis, reported an incidence of cirrhosis of 10.3 per 100,000 population aged 15 years and over from patients diagnosed in a single district general hospital in west Birmingham and from Coroner's post-mortem reports. Though representative of the population served by this hospital, these figures are not generalisable to the rest of the UK as the West Midlands region has a higher than average mortality from liver disease compared with the general population of the UK.[39] With any hospital-based series there is the potential for an ascertainment bias with active case finding being employed, leading to a further over-estimate of incidence. In addition, in the study by Saunders et al, 11.3% of the subjects included as incident cases were as a result of incidental findings at post-mortem examination. The same factors are unlikely to have operated in my study.

The results displayed in this study show a higher or similar incidence of cirrhosis compared with the previous studies of cirrhosis in the UK[37 38 40] but owing to the small, non-representative nature of these studies, and a lack of clarity as to exact methods used, direct comparisons should be avoided. This study is the only study based on a contemporary, representative sample of the entire UK population and has utilised data collected for general medical purposes over a period of 10 years.

My data contrast with recent data from a hospital-based study in Denmark where no discernible trend in incidence of alcoholic cirrhosis was seen from 1994-2005.[45] The figures reported in this study similarly showed a higher incidence and prevalence of cirrhosis for men than women, and for those aged between 45 and 64 years of age, although the crude incidence figures for alcoholic cirrhosis were higher than I saw in my study. Other data from Scandinavia report similar figures to those reported in this chapter for Gothenburg, Sweden (incidence of 15.3 per 100,000 person years)[85] and Oslo, Norway (incidence of 13.3 per 100,000 person years)[86] but a much lower incidence for Iceland (incidence of 3.3 per 100,000 person years).[85]

I have presented the first data quantifying the current burden of alcoholic cirrhosis in the UK but it is important to note that the incidence of non-alcohol related cirrhosis also increased over this period. Though it is possible that some of these cases were indeed misclassified alcoholic cirrhosis, it is also possible that other causes of cirrhosis are also on the increase. From a public health perspective a particularly important and potentially modifiable set of risk factors are those of obesity and its relationship with type 2 diabetes. Where fatty liver leads to steatohepatitis, fibrosis can occur in roughly one third of patients.[20] In one study, a history of obesity and/or type 2 diabetes was found

in 73% of patients with 'cryptogenic' cirrhosis.[87] Although cirrhosis is far from recognised as an end-point for diabetes or obesity the sustained increase in these two potential risk factors may lead to further increases in the incidence of cirrhosis in the UK in the years to come.

3.4.4 Conclusions

Liver disease is one of very few chronic diseases where mortality in the UK has increased over the past three decades.[88] In contrast, mortality from ischaemic heart disease, cerebrovascular diseases and respiratory diseases have all decreased. With a minimum estimate of 31,000 people over the age of 25 living with cirrhosis, a figure which is likely to increase, and with no good treatment options other than liver transplant, mortality from this disease will continue to rise.

Although the accuracy of defining true incidence is somewhat difficult with a chronic condition with heterogeneic presentation such as cirrhosis the figures reported in this study represent the most up-to-date estimates of the absolute rates and trends in incidence and prevalence of cirrhosis in the UK having used population-based data over a period of 10 years.

Cirrhosis represents a serious and growing burden of morbidity in the general population of the UK. The continued rise in cirrhosis has significant implications for the provision of specialist services and the health of the nation.

4 All-cause mortality in people with cirrhosis compared with the general population

4.1 Introduction

This study aims to describe the mortality experience of people with cirrhosis with reference to a general population cohort without cirrhosis.

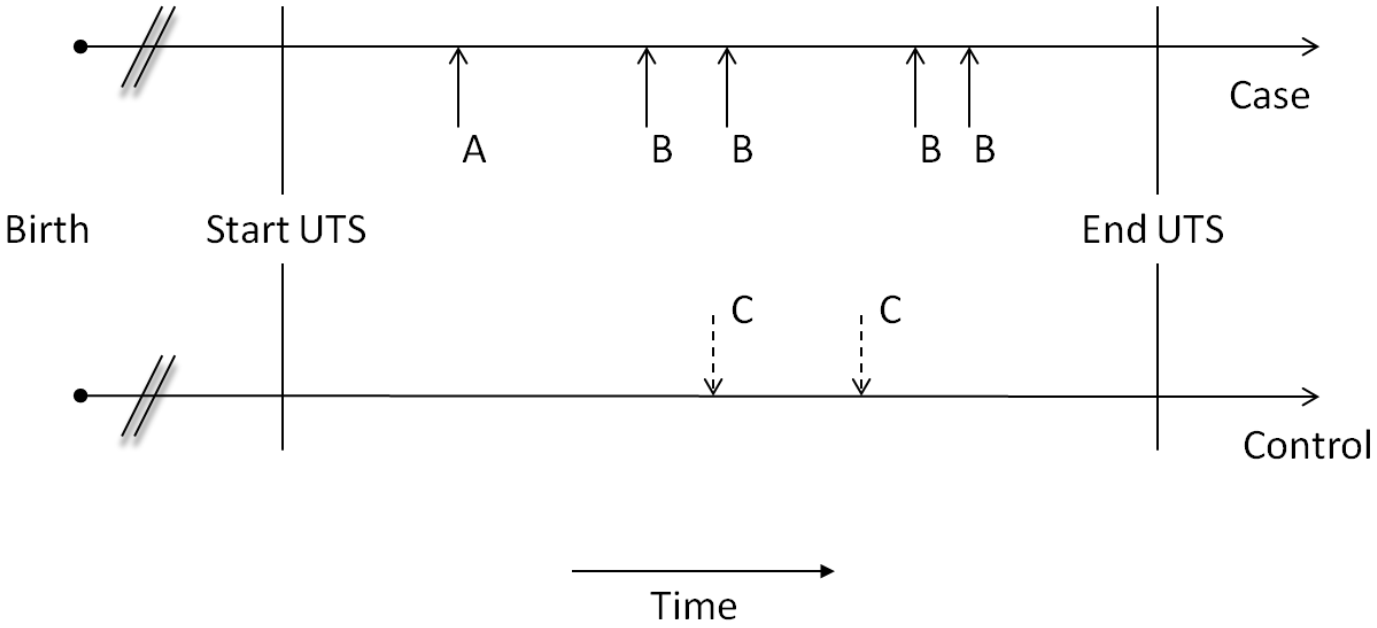
4.2 Methods

4.2.1 Dataset used

The data used in this chapter were from all subjects with a diagnosis of cirrhosis (as described in section 2.4.3) and their matched controls. By definition these controls were initially selected based on the exclusion of the first recorded liver disease within their matched case (see section 2.4.1). It was therefore possible that a control subsequently had a diagnosis of a liver disease other than the liver disease that first identified their matched case's record (see Figure 4-1). As cirrhosis was potentially not the first liver disease that a case was diagnosed with I excluded controls who

a) had cirrhosis as a diagnosis at any point in their GPRD record, or

b) were not alive at the time of diagnosis of cirrhosis in their matched case.



A. Identification of case's first liver disease within UTS period. Control is free of this disease for whole UTS period.
B. Further codes for liver disease within case's record. At least one of these must represent cirrhosis.
C. Codes for liver disease within control's record

Figure 4-1 Time-line showing potential diagnosis of cirrhosis in control subjects.

4.2.2 Additional definitions

4.2.2.1 Date of diagnosis / pseudo-diagnosis

Cases were assigned a date of diagnosis as the first recorded date of any of the codes for cirrhosis in their general practice record (see section 2.4.3). Matched controls were then given this date as their date of 'pseudo-diagnosis'.

4.2.2.2 Age

Age at diagnosis, or pseudo-diagnosis for controls, was categorised into 25-44 years, 45-64 years and 65 years and above for the purposes of analysis.

4.2.2.3 Body Mass Index

Body Mass Index (BMI in kg/m^2) was defined using data on height, weight and/or BMI contained within the prevention data file. Data on height and weight contained several outliers of implausibly low or high values, mostly of an order of magnitude of 100 or 1000 times normal plausible values suggesting transcription errors in the number of zeroes recorded. Consequently weights of greater than 300kg or less than 30kg, heights of greater than 2.5m or less than 1m, and BMI values of greater than 100 were excluded. Values of height and weight recorded at least one year before the date of diagnosis of cirrhosis for cases or date of pseudo-diagnosis for controls were then examined and the median value of each used to calculate the BMI of the patient. Where there was a value for a patient's BMI, again recorded at least one year before the date of diagnosis of cirrhosis or pseudo-diagnosis, this was used in preference to a calculated value using height and weight measurements. The 1-year cut off was used to try to ensure weight loss due to undiagnosed disease did not change the initial BMI categorisation of subjects.

BMI was then categorised according to recognised clinically meaningful limits: <18.5 (underweight), 18.5-24.9 (ideal weight), 25.0-29.9 (overweight), 30.0-34.9 (obese) and 35.0+ (severely obese).

4.2.2.4 Smoking

Smoking status was ascribed using a combination of medical codes for smoking contained within the medical data file and information recorded within the prevention file on the number of cigarettes smoked before the date of diagnosis or pseudo-diagnosis. Smoking codes in a subject's medical file were categorised as 'Non-smoker', 'Ex-smoker or 'Smoker' (see

) If there was more than one category coded in a subject's record, subjects were assigned the category that indicated greatest smoking experience during their record.

4.2.2.5 Alcohol use

Alcohol use was observed in two ways. Firstly, looking at the alcohol consumption data from the prevention data file the number of units of alcohol consumption in a week was extracted. Secondly, information on recorded alcohol status, prior to diagnosis, was extracted from the medical file using the codes for alcohol use (see Appendix III-c Codes for alcohol use).

4.2.2.6 Comorbidity

Comorbidity was described using a composite measure of illnesses diagnosed in each patient, based on the Charlson score.[89] The original Charlson score includes a category for mild liver disease as a weighted score of 1 and a category for moderate or severe liver disease as a weighted score of 3 (see Table 4-1). For this study I excluded liver disease from the comorbidity score. For the purposes of this study diseases had to be identified prior to the date of

diagnosis or pseudo-diagnosis. Particular diseases were identified from data contained within the medical file, weighted and a comorbidity score derived (see Appendix III-j Codes for comorbidity). Scores were then categorised as 0, 1, or 2+ for the purposes of analysis. This has subsequently been validated by others as a good predictor of mortality in the GPRD.[90]

Table 4-1 Charlson score – weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease *Mild liver disease (Not included in this study*) Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	*Moderate or severe liver disease* *(Not included in this study)*
6	Metastatic solid tumour AIDS

4.2.2.7 Liver transplant

For the end-point of some of the analyses I included liver transplant as well as death. Liver transplant was defined using medical codes from the medical file (see Appendix III-k Codes for liver transplant).

4.2.2.8 Compensated and decompensated disease

Cases were classified as being in a compensated or decompensated disease state at the date of diagnosis. Cases with a code for ascites or gastrointestinal bleed at or before the date of diagnosis were classified as being in a decompensated disease state (see Table 4-2).

4.2.2.9 Aetiology of cirrhosis

Aetiology was ascribed as per the methods in section 3.2.2.2.

Table 4-2 Medical codes for ascites and GI bleed (decompensated disease)

Description	medcode
[D]ASCITES	R095.00
[D]ASCITES NOS	R095z00
[D]FLUID IN PERITONEAL CAVITY	R095000
ACUTE GASTRIC ULCER WITH HAEMORRHAGE	J110100
ACUTE GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	J110300
BLEEDING ACUTE GASTRIC ULCER	J110111
BLEEDING CHRONIC DUODENAL ULCER	J121111
BLEEDING CHRONIC GASTRIC ULCER	J111111
CHRONIC DUODENAL ULCER WITH HAEMORRHAGE	J121100
CHRONIC DUODENAL ULCER WITH HAEMORRHAGE AND PERFORATION	J121300
CHRONIC GASTRIC ULCER WITH HAEMORRHAGE	J111100
CHRONIC GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	J111300
CHYLOUS ASCITES	457 CA
CHYLOUS ASCITES	G86y100
DRAINAGE OF ASCITES NEC	7H2B200
GASTROINTESTINAL HAEMORRHAGE UNSPECIFIED	J68z.00
GASTROTOMY AND LIGATION OF BLEEDING POINT OF STOMACH	7619100
GI BLEEDING	569 M
GIB - GASTROINTESTINAL BLEEDING	J68z.11
HAEMATEMESIS	J680.00
HAEMORRHAGE GASTROINTESTINAL	569 MI
HEPATIC ASCITES	5719AH
INSERTION OF DENVER PERITONEOVENOUS SHUNT	7H2B111
INSERTION OF LE VEEN PERITONEOVENOUS SHUNT	7H2B112
INSERTION OF PERITONEAL TO VENOUS SHUNT FOR ASCITES	7H2B113
INTESTINAL HAEMORRHAGE	569 MH
MELAENA	J681.00
OESOPHAGEAL VARICES WITH BLEEDING	G850.00
OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	G852000
OESOPHAGUS BLEEDING	5309H
OESOPHAGUS HAEMORRHAGE	5309HA
O/E - ASCITES	25O..00
O/E - ASCITES - DIPPING SHOWN	25O2.00
O/E - ASCITES NOS	25OZ.00
O/E -ASCITES-SHIFTING DULLNESS	25O4.00
O/E-ASCITES-FLUID THRILL SHOWN	25O3.00
PARACENTESIS ABDOMINIS FOR ASCITES	7H2B000
PERITONEAL TO VENOUS DRAINAGE FOR ASCITES	7H2B100
TANNER DEVASCULARISATION FOR BLEEDING VARICES	7609y11
UPPER GASTROINTESTINAL HAEMORRHAGE	569 ME
VOMITING OF BLOOD	J680.11

4.2.3 Statistical analysis

Using Cox proportional hazards regression I modelled the hazard of death in the cirrhosis cohort (classifying subjects with cirrhosis as either compensated or decompensated at entry (as described in section 4.2.2.8)) compared with the control cohort employing an historical matched cohort study design. Subjects with cirrhosis and controls entered the analysis period at the date of diagnosis or pseudo-diagnosis respectively and exited at the earliest of either date of death, deregistration with their general practice or 30 April 2002 which was the last date of available data in this dataset. This principal analysis was adjusted, a priori, for age and sex. Additional potential confounders (BMI, smoking, alcohol intake and comorbidity group) were modelled as categorical variables (with a separate category for missing data) and included in the final Cox model if they conferred a 10% or greater adjustment in the hazard ratios seen.

Owing to the probable high influence of comorbidity on mortality, particularly at early stages, I split follow up time at 1 year and modelled hazard ratios during the first year following diagnosis and after 1 year stratified by comorbidity.

I then split the population of cases into those with alcoholic cirrhosis and those with non-alcohol related cirrhosis (as described in section 3.2.2.2) and examined the mortality rates and adjusted hazard ratios compared with their matched controls for these two aetiologic groups.

To minimise the potential for survival bias I ran the principal analysis again comparing mortality between compensated and decompensated cases and controls using all incident cases (as described in section 3.2.2.1) and their matched controls. To try to account for potential attrition bias I also ran the principal analysis using the earliest of date of death, deregistration or last

recorded appointment in the GPRD as the exit-point for the analysis. Finally, the principal analysis was repeated using death and liver transplant as the end-point for the Cox model.

Proportional hazards assumptions were checked using Schoenfeld residuals and log-log plots.

4.3 Results

A total of 4537 subjects with cirrhosis and 44,403 appropriately matched controls contributing a total of 226,412 person years of follow-up were included within this analysis, with a median follow-up time of 3.5 years per patient.

4.3.1 Population characteristics

As would be expected due to the method of control selection the cirrhosis cohort and the control cohort had very similar age distributions and sex profile (see Table 4-3). Most of the subjects in both the cirrhosis and control cohorts had no recorded comorbidity prior to diagnosis. Subjects with cirrhosis were slightly more likely to have some recorded comorbidity than controls. Notably there was a high proportion of missing data in both cohorts for BMI, smoking status and alcohol consumption (as measured by unit intake). Subjects with cirrhosis were much more likely to have a recorded alcohol status (as per codes within the medical file) than controls prior to the date of diagnosis (or pseudo-diagnosis).

There were few liver transplants recorded with only 2.3% of all cirrhosis subjects having a liver transplant subsequent to diagnosis with cirrhosis. Just over four-fifths of the cirrhosis cohort entered the analysis in a compensated state of disease. Just over half of the cirrhosis subjects (50.9%) had alcohol as their presumed aetiology (when taking into account recording of alcohol problems at any point in the record).

Table 4-3 Demographic, lifestyle and clinical characteristics of cirrhosis cohort and general population cohort

	Cirrhosis Cohort (N=4537)	Control Cohort (N=44 403)
Demographics / lifestyle factors		
Age at diagnosis (years)		
Median age [IQR]	56.5 [46.9, 67.0]	56.2 [46.8, 66.8]
(range)	(25.2, 99.6)	(25.2, 102.9)
25-44	943 (20.8)	9403 (21.2)
45-64	2256 (49.7)	22 219 (50.0)
65+	1338 (29.5)	12 781 (28.8)
Sex		
Male	2612 (57.6)	25 599 (57.7)
Female	1925 (42.4)	18 804 (42.3)
BMI		
Median BMI [IQR]	25.5 [22.5, 28.7]	25.3 [23, 28.2]
No recorded BMI	3624 (80.0)	33 294 (75.0)
Smoking status (prior to diagnosis)		
No smoker	10 (0.2)	92 (0.2)
Ex-smoker	15 (0.3)	113 (0.3)
Smoker	387 (8.5)	2461 (5.5)
Missing	4125 (90.9)	41 737 (94.0)
Alcohol consumption (units)		
Median consumption per week [IQR] (range)	7 [0, 29] (0, 400)	2 [0, 10] (0, 700)
Mean unit intake (sd)	20.8 (33.7)	7.2 (14.5)
No recorded unit intake	2577 (56.8)	22 792 (51.3)
Alcohol status (prior to diagnosis)		
Non-drinker	2 (<0.1)	10 (<0.1)
Drinker	170 (3.8)	1007 (2.3)
Alcoholic	1377 (30.4)	740 (1.7)
Not recorded	2988 (65.9)	42 646 (96.0)
Comorbidity score		
0	3525 (77.7)	37 085 (83.5)
1	534 (11.8)	3704 (8.3)
2+	478 (10.5)	3614 (8.1)
Clinical characteristics		
Liver transplants	105 (2.3)	2 (<0.1)
Disease state at entry		
Compensated	3660 (80.6)	
Decompensated	877 (19.4)	-
Presumed Aetiology†		
Alcoholic	2307 (50.9)	
Viral hepatitis	238 (5.3)	
Metabolic liver disease	48 (1.1)	-
Autoimmune liver disease	354 (7.8)	
No specified aetiology	1730 (38.1)	

†as a case could have more than one presumed aetiology numbers in the table do not necessarily add up to 4537.

4.3.2 Cox regression modelling

4.3.2.1 Overall survival

When building the Cox regression model only the a priori confounders of age and sex remained in the model.

Overall, patients with cirrhosis had a hazard ratio for death (adjusted for age and sex) of 5.8 (95%CI[5.5, 6.1]) compared with the general population cohort (see Table 4-4). A still higher hazard ratio for death was seen in patients with decompensated disease compared with the general population with an adjusted hazard ratio of 9.6 (95%CI[8.7, 10.7]) but a significantly higher hazard of death was still seen for patients with compensated disease with an adjusted hazard ratio of 5.2 (95%CI[4.9, 5.5] (see Figure 4-2).

Crude survival at 1 and 5 years was correspondingly lower for patients with decompensated disease (76.4% (95%CI[73.3%, 79.2%]) and 45.2% (95%CI[40.9%, 49.3%]) respectively) than for patients with compensated disease (85.2% (95%CI[84.0%, 86.3%]) and 63.5% (61.5%(95%CI[61.5%, 65.3%]) respectively). For all patients with cirrhosis survival was 83.5% (95%CI [82.4, 84.6]) at 1 year and 60.1% (95%CI [58.3, 61.8]) at 5 years compared with 98.0% (95%CI [97.9, 98.1]) and 90.7% (95%CI [90.3, 91.0]) respectively for the control population.

Table 4-4 Cox proportional hazards model for overall mortality

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
Controls	4033	209 554	19.2 [18.7, 19.8]	-	-
All cirrhosis	1769	16 858	104.9 [100.1, 109.9]	5.4 [5.1, 5.7]	5.8 [5.5, 6.1]
Compensated cirrhosis	1360	14 560	93.4 [88.6, 98.5]	4.8 [4.5, 5.1]	5.2 [4.9, 5.5]
Decompensated cirrhosis	409	2298	178.0 [161.5, 196.1]	8.8 [8.0, 9.8]	9.6 [8.7, 10.7]

*adjusted for age and sex

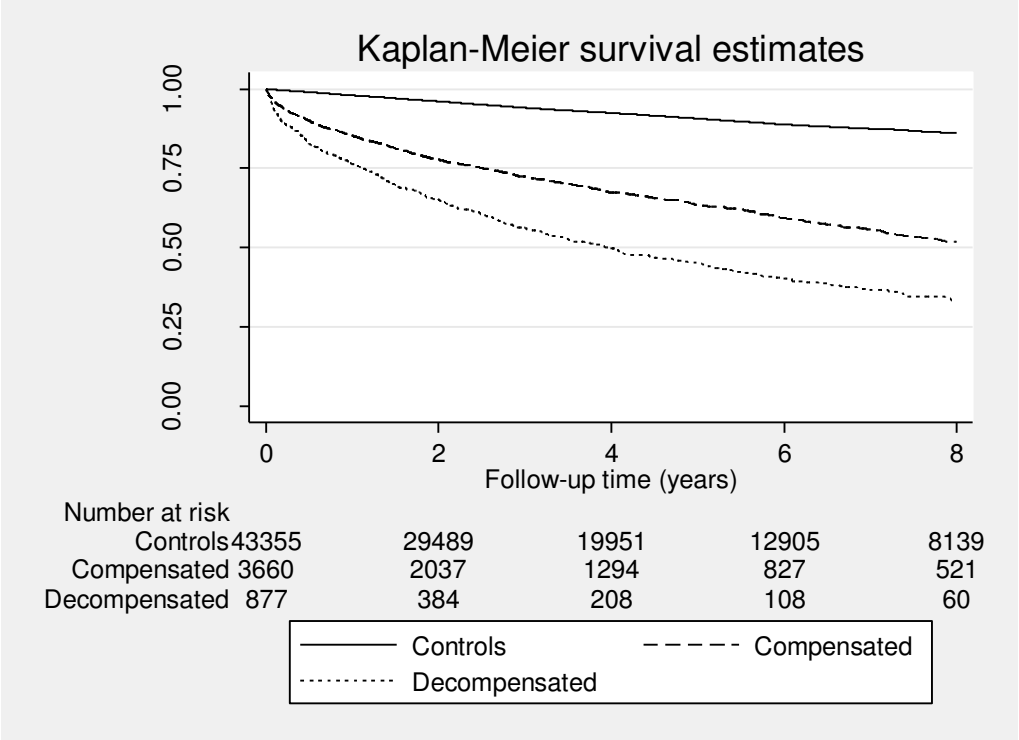


Figure 4-2 Survival estimates for controls, subjects with compensated cirrhosis and subjects with decompensated cirrhosis.

4.3.2.2 Testing the proportional hazards assumptions

Examination of the log-log plot and the plot of Schoenfeld residuals against time showed that there was a significant decrease in the hazard of death in the first year or so of follow-up (see Figure 4-3, Figure 4-4). As I had already planned to split follow-up time at one year I present all the remaining results as mortality during the first year and mortality subsequent to the first year.

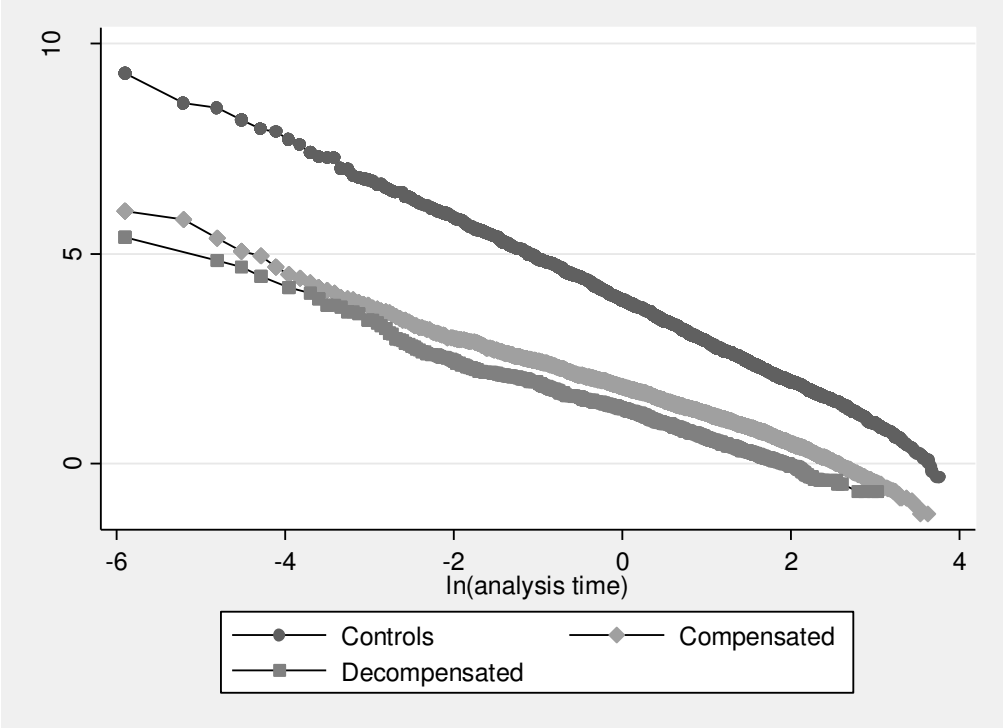


Figure 4-3 Log-log plot for overall mortality analysis

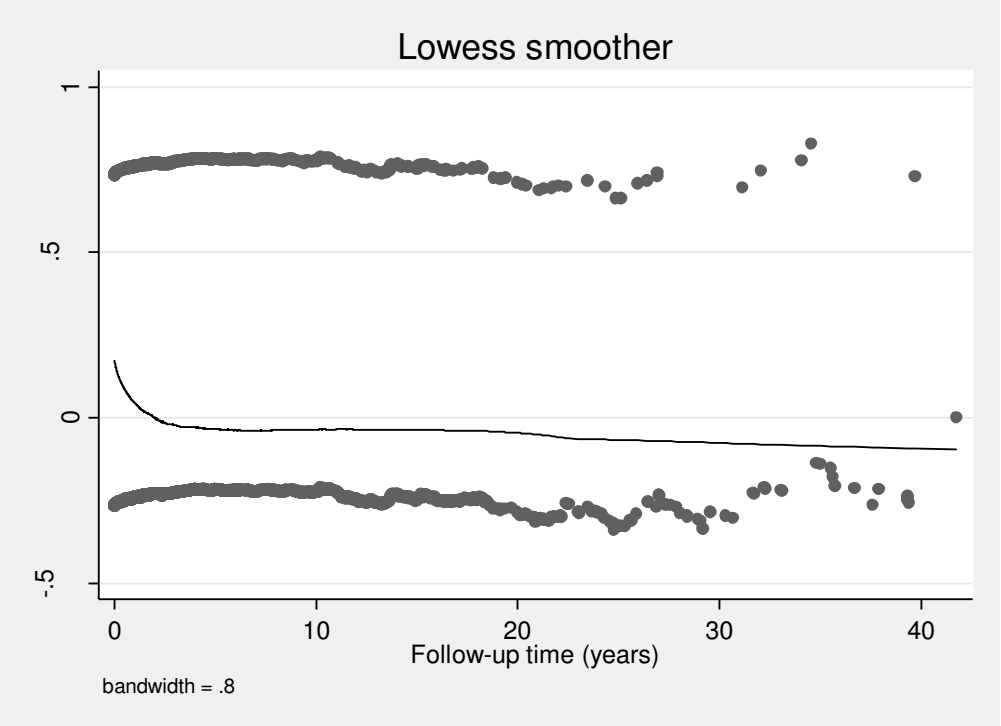


Figure 4-4 Schoenfeld residuals against time for overall mortality

4.3.2.3 Survival by follow-up and comorbidity score

Mortality for subjects with cirrhosis was higher during the first year following diagnosis than subsequently but also remained substantial beyond one year (see Table 4-5). Stratification by comorbidity showed that although the absolute mortality rates were lowest in those with no recorded comorbidity the adjusted hazard ratios for death were highest in this group. This high relative risk of death was most noticeable in the first year following diagnosis with hazard ratios of 8.5 for the compensated cohort compared with the general population and 14.2 for the decompensated cohort, approximately double those seen in the years following the first year after diagnosis.
Comorbidity appeared to have more of an influence on the mortality of the subjects with compensated disease than those with decompensated disease.

Table 4-5 Overall mortality analysis split by follow-up time and stratified by Charlson index

	Mortality rate (per 1000)			Adjusted hazard ratio *	
	Control cohort	**Compensated cohort**	**Decompensated cohort**	**Compensated cohort**	**Decompensated cohort**
During first year					
Overall	20.1	167.1	288.1	8.5 [7.6, 9.5]	14.2 [12.1, 16.6]
Charlson score					
0	16.5	159.1	266.3	9.9 [8.7, 11.2]	16.6 [13.7, 20.3]
1	28.6	174.8	249.0	6.8 [4.9, 9.4]	9.3 [6.0, 14.3]
2+	49.5	233.9	424.5	4.8 [3.5, 6.4]	8.9 [6.4, 12.5]
Following first year					
Overall	19.0	73.8	133.0	4.3 [3.9, 4.6]	7.9 [6.9, 9.1]
Charlson score					
0	16.4	70.6	118.9	4.7 [4.3, 5.1]	8.3 [7.0, 9.8]
1	32.8	90.3	126.0	3.2 [2.6, 4.1]	5.2 [3.6, 7.4]
2+	43.0	94.6	246.1	2.4 [1.8, 3.1]	7.2 [5.2, 10.0]

*adjusted for age and sex

4.3.2.4 Survival by presumed aetiology

As might be expected following the previous analysis mortality during the first year for both alcoholic cirrhosis and non-alcohol related cirrhosis was higher than in subsequent years (see Table 4-6).

The absolute mortality rate of subjects with non-alcohol related cirrhosis was higher than that of subjects with alcoholic cirrhosis in the first year following diagnosis. Subsequent to the first year mortality was similar in both groups. However, the adjusted hazard ratios for mortality were much higher in the subjects with alcoholic cirrhosis compared to those with non-alcohol-related cirrhosis. This is a result of the absolute mortality rates seen in the control population. The matched controls of subjects with alcoholic cirrhosis had a considerably lower mortality than the matched controls of subjects with non-alcohol related cirrhosis. Examining the age and sex distribution of the patients with cirrhosis showed a significantly higher age at diagnosis for subjects with non-alcohol related cirrhosis compared to those with alcoholic cirrhosis (see Table 4-7).

The age- and sex-adjusted hazards ratios for subjects with alcoholic cirrhosis following the first year after diagnosis were similar to those of non-alcohol related cirrhosis during the first year following diagnosis.

Table 4-6 Mortality split by follow-up time and stratified by alcoholic aetiology

	Events	Person-years	Mortality rate (per 1000 person years)	Adjusted hazard ratio* [95%CI]
During first year				
Alcoholic cirrhosis				
Controls	271	20 344	13.3 [11.8, 15.0]	-
Compensated cirrhosis	234	1519	154.1 [135.5, 175.1]	11.8 [9.9, 14.1]
Decompensated cirrhosis	94	393	239.0 [195.2, 292.5]	17.6 [13.9, 22.2]
Non-Alcohol-related cirrhosis				
Controls	525	19 257	27.3 [25.0, 29.7]	-
Compensated cirrhosis	278	1544	180.0 [160.0, 202.4]	6.9 [5.9, 7.9]
Decompensated cirrhosis	98	273	358.9 [294.4, 437.4]	12.3 [9.9, 15.3]
Following first year				
Alcoholic cirrhosis				
Controls	1181	90 469	13.1 [12.3, 13.8]	-
Compensated cirrhosis	465	5825	79.8 [72.9, 87.4]	6.4 [5.7, 7.1]
Decompensated cirrhosis	128	960	133.3 [112.1, 158.5]	12.4 [10.3, 14.9]
Non-Alcohol-related cirrhosis				
Controls	2056	79 485	25.9 [24.8, 27.0]	-
Compensated cirrhosis	383	5671	67.5 [61.1, 74.6]	3.1 [2.7, 3.4]
Decompensated cirrhosis	89	671	132.6 [107.7, 163.2]	5.2 [4.2, 6.4]

*adjusted for age and sex

Table 4-7 Sex and age distribution of subjects with alcoholic and non-alcohol-related cirrhosis

	All cirrhosis N=4537 n(%)	Alcoholic cirrhosis N=2307 n(%)	Non-alcohol-related cirrhosis N=2230 n(%)
Sex			
Male	2612 (57.6)	1528 (66.2)	1084 (48.6)
Female	1925 (42.4)	779 (33.8)	1146 (51.4)
Age (in years)			
Median [IQR]	56.5 [46.9, 67.0]	51.7 [44.1, 60.5]	62.6 [52.0, 71.9]
25-44	943 (20.8)	643 (27.9)	300 (13.5)
45-64	2256 (49.7)	1311 (56.8)	945 (42.4)
65+	1338 (29.5)	353 (15.3)	985 (44.2)

4.3.2.5 Cox proportional hazards model using different cohort definitions

Running the analyses using an incident cohort, censoring subjects at the date of their last appointment within the GPRD, or using death or liver transplant as the end-point led to no substantial differences in the adjusted hazard ratios for mortality either during the first year following diagnosis or subsequently (see Table 4-8).

Analysis using an incident cohort restricted the number of cases to 2787 and 26,176 appropriately matched controls. I showed a slightly higher hazard of death for subjects with compensated cirrhosis both during the first year following diagnosis and subsequently compared to the initial analysis including both prevalent and incident cases. Patients with decompensated disease showed a slightly lower hazard of death in the first year following diagnosis but a greater hazard of death subsequently compared to the initial analysis.

When censoring subjects at either death, de-registration or date of last appointment within the GPRD (as opposed to the end of the UTS period) there was a slightly lower hazard of death for both subjects with compensated and decompensated disease at both time periods studied compared to the initial analysis.

For the analysis using death and liver transplant as the outcome there was a slight increase in the adjusted hazard ratios for death in all subjects at both time periods studied compared with the initial analysis.

None of the hazard ratios observed in any of these three variations on analysis led to any significant differences to those calculated from the initial analysis.

Table 4-8 Cox proportional hazards model using different cohort definitions

	Mortality rate (per 1000)			Adjusted hazard ratio *	
	Control cohort	**Compensated cohort**	**Decompensated cohort**	**Compensated cohort**	**Decompensated cohort**
During first year					
Principal analysis	**20.1**	**167.1**	**288.1**	**8.5 [7.6, 9.5]**	**14.2 [12.1, 16.6]**
Incident cohort	24.1	212.3	309.7	9.0 [7.9, 10.2]	13.1 [11.0, 15.8]
Censoring at last GPRD appointment	22.5	171.1	293.8	7.9 [7.1, 8.9]	13.2 [11.3, 15.5]
Death and liver transplant end point	20.1	172.8	300.1	8.8 [7.8, 9.8]	14.7 [12.6, 17.2]
Following first year					
Principal analysis	**19.0**	**73.8**	**133.0**	**4.3 [3.9, 4.6]**	**7.9 [6.9, 9.1]**
Incident cohort	22.7	96.1	158.1	4.6 [1.4, 5.1]	8.8 [7.4, 10.5]
Censoring at last GPRD appointment	21.3	75.8	137.2	4.0 [3.7, 4.3]	7.4 [6.5, 8.5]
Death and liver transplant end point	19.1	80.6	142.0	4.6 [4.3, 5.0]	8.3 [7.2, 9.5]

*adjusted for age and sex

4.4 Discussion

4.4.1 Key findings

Patients with a diagnosis of cirrhosis are at an increased risk of death than their age- and sex-matched general population controls with an adjusted hazard ratio for death of 5.8 (95%CI[5.5, 6.1]). Those with decompensated disease have an even worse prognosis with 5- year survival only 45.2% compared with 63.5% for those with compensated disease. The increased risk of death was particularly high during the first year following diagnosis but remained high subsequently, even following adjustment for some measure of comorbidity. The hazard ratio for death was highest in those with no reported comorbidity although absolute mortality rates were highest in those with reported comorbidities. Patients with a presumed aetiology of alcoholic cirrhosis had a worse survival at all stages than those with non-alcohol related cirrhosis.

4.4.2 Strengths and limitations

This study has been performed using a large, representative, population-based cohort of patients with cirrhosis alongside an appropriately matched general population based control cohort. These cohorts were identified relatively recently (1987 – 2002) and the results observed reflect the natural history of cirrhosis during this time period.

The size of the dataset used for this analysis has allowed the estimation of mortality rates and adjusted hazard ratios for death stratifying by severity of disease, follow-up time and comorbidity.

Perhaps the most significant potential limitation of this analysis is related to the coding of the diagnosis of cirrhosis. As discussed in section 3.4.2 the inclusion of all patients with any mention of cirrhosis, oesophageal varices or portal hypertension within the medical records may have led to the inclusion of some patients who did not have cirrhosis. However, the same counter-argument is applicable in this situation that it is more likely that there are cases with cirrhosis that are missing from the data source where the diagnosis of cirrhosis was unconfirmed and / or not fed back from secondary care to primary care records. This will potentially have led to an underestimate of the hazard ratio for death as cases with undiagnosed cirrhosis may be included within the control population.

In addition to the potential for misclassification of the diagnosis of cirrhosis it is possible that there exists further misclassification in the accuracy of the severity of cirrhosis as compensated or decompensated. Whilst the results of the validation described in section 3.3.4 lend credence to the diagnosis of cirrhosis itself, with evidence that most diagnoses occurred in secondary care, the prohibitive cost of validation within the GPRD system did not allow for the validation of the additional signs and symptoms of ascites and gastrointestinal bleeding used to define decompensated disease. Indeed, these clinical symptoms may only be recorded if they are of obvious clinical relevance to the GP. Ascites and gastrointestinal bleeding are however serious complications of cirrhosis and as such one might expect that these events would be considered important and therefore recorded within the primary care record, either following hospital correspondence or from an individual patient consultation. It is possible that the recording of ascites, if it occurred in the absence of further information from hospital, would only be large-volume, clinically significant ascites visible at the general practice appointment rather than that only identified by ultrasound. Assuming that the misclassification is

most likely to act through misclassifying patients with decompensated cirrhosis as having compensated disease this will have led to an overestimate of the hazard ratios for death for people with compensated disease and a corresponding underestimate of the hazard ratios for death for people with decompensated disease.

The size of the database used has allowed the description of the mortality experience of patients with both alcoholic and non-alcohol related cirrhosis alongside their matched controls. The small numbers of cases with other presumed aetiologies meant that it was not possible to model the hazard of death for other causes of cirrhosis with any precision.

It could be argued that the inclusion of both incident and prevalent cases in the cirrhosis cohort might lead to the introduction of survival bias as those cases who are prevalent have, by definition, already survived a particular length of time to still be included in the analysis. As such, I ran the principal analysis using only those subjects who were considered incident as defined in section 3.2.2.1. The estimates of the mortality rates and therefore the hazard ratios for death were slightly higher than those seen when including all incident and prevalent cases, apart from subjects with decompensated disease in the first year following diagnosis who showed a slightly lower hazard ratio for death. However, all estimates remained within the 95% confidence interval of the principal analysis. The results I have reported including all incident and prevalent cases probably more accurately reflects the real world of clinical practice within the general population and allows for the communication of results that are directly valid to the patients an individual GP may see in their practice.

Though the data available have allowed for an appropriate individually-matched adjustment for some confounders (age and sex) it was not possible to examine the potential associations or modifying effects of other variables either because they are not available in the GPRD at all e.g. any measure of socio-economic status which is known to be associated with mortality, or because there was such a high proportion of missing data. Recent studies have suggested an interaction between raised BMI and alcohol consumption leading to an increased risk of death from liver disease.[91] Additionally it was not possible within this dataset to examine the cause of death of these patients as this information was not systematically available.

Of note is the discrepancy in the proportion of patients who were recorded to be alcoholics before the diagnosis of cirrhosis (30.4%) and the proportion of patients assigned a presumed aetiology of alcoholism (50.9%). Aetiologies were ascribed using information contained in the whole medical record (including after the diagnosis of cirrhosis). This would therefore suggest that roughly two-fifths of those patients with alcoholic cirrhosis were not known to be (or at least not recorded as) alcoholics before the onset of their disease. However, when taken in context to the 96.0% of controls who did not have their alcohol status recorded before the date of pseudo diagnosis, it is perhaps encouraging that so many patients with cirrhosis had already been identified as alcoholics.

4.4.3 Comparison with previously published work

In the UK the most recent published study on cirrhosis mortality observed the mortality of patients with all chronic liver disease who had been admitted to hospital in a small geographically distinct region of the UK between 1968 and 1999.[41] This study reported an SMR for one year follow-up of 16.3. This figure is higher than the 1-year adjusted hazard ratios that I have reported for either patients with compensated or decompensated disease.

Other large cohort studies from European centres have similarly shown worse survival than I have reported in this chapter. In Denmark between 1995 and 2006 a hospital cohort of 14,976 patients with cirrhosis described a 1-year survival of only 65.5% and 5-year survival of 37.5%, notably lower than that I have reported.[92] This study was not able to categorise patients into compensated or decompensated disease and additionally did not report the hazard ratios for mortality compared with their matched control cohort. Previously the same authors had reported SMRs for patients hospitalized with cirrhosis compared with the general population of 32.3 for the first year following diagnosis and 5.7 thereafter.[46]

These poorer survival estimates are perhaps unsurprising as these previous studies used cohorts of patients admitted to hospital. Whilst the diagnosis of cirrhosis in my study population is likely to have come from a hospital diagnosis it does not necessarily follow that these patients were hospitalized for this diagnosis to occur. As my study is a population-based cohort the results seen are also unlikely to have been affected by the variation in referrals and follow-ups seen in cohorts selected from secondary care. As such it is probable that my results can be more widely generalised to patients diagnosed with cirrhosis including those ambulatory patients who have not been admitted to hospital.

Perhaps the most commonly referenced figures in the literature looking at the mortality experience of patients with cirrhosis based on the severity of disease are those based on 1155 consecutive patients admitted to a single hospital in Sicily during the 1970s and 1980s which reported 6-year survival of 54% and 21% in patients with compensated and decompensated cirrhosis respectively.[44] It is possible that the survival figures I report are better than those reported in this smaller study, particularly for those patients with decompensated disease, because there have been significant improvements in the management and outcomes of the complications of cirrhosis in the intervening decades. This has been shown for oesophageal varices in studies in both the USA and more recently Sweden.[58 60] Additionally, the proportion of cases ascribed as alcoholic cirrhosis is lower in the Sicilian population than in my study population with a correspondingly higher proportion of patients with hepatitis B virus. It is therefore possible that the survival figures reflect a different spectrum of aetiology of cirrhosis in the two populations.

Other estimates of mortality in patients with cirrhosis in the UK come from much older studies. Saunders et al report the 5-year survival of patients with alcoholic cirrhosis, 36%, and non-alcohol related cirrhosis, 14%.[37] An earlier study, also from Birmingham, covering patients with cirrhosis in a single hospital between 1959-64 reports similarly low 5-year survival figures of 14.4% after first admission to hospital, again with patients with alcoholic cirrhosis having a better prognosis (5-year survival of 20% compared with 5.1% for patients with cryptogenic cirrhosis).[43]

The survival figures I have reported are better than these two previous studies but conversely show that survival with non-alcohol related cirrhosis confers a lower risk of mortality than that seen with an alcoholic aetiology.

4.4.4 Conclusions

In this study I have shown that the survival of patients with a diagnosis of cirrhosis, whilst better than previously reported studies,[37 41 43 44 45 46 47 48 57 93] is still poor with 1-year survival of 83% and 5-year survival of 60%. This study represents the most contemporary estimate of the mortality experience of patients with cirrhosis and also allows comparison with the general population. Even in those patients with no comorbidity the adjusted hazard ratio for death is significantly higher than that of the general population.

I have been able to describe the mortality experience of patients with compensated and decompensated disease, showing a substantial increase in mortality for those with decompensated disease at diagnosis.
Defining decompensated cirrhosis as the presence of ascites or GI bleeding appears to accurately reflect an increased probability of death compared to compensated cirrhosis. Although there is the possibility of misclassification of patients with decompensated disease as compensated as differences in follow-up at individual sites may exist, these general population based data provide an 'average' estimate of the mortality experienced by patients with cirrhosis. These figures will be of particular importance for service providers and for individual clinicians and general practitioners to communicate to their patients.

For the purposes of service provision and planning it is important to note that even patients with compensated disease had an increased hazard of death compared to the general population. This is in contrast to the assumptions made for the purposes of the cost-effectiveness analysis carried out in a recent HTA systematic review where it was claimed that existing data suggest

that there is no excess mortality in those patients with compensated disease compared with the general population.[49]

An aetiology of alcoholic cirrhosis remains a particularly bad prognostic indicator with mortality in patients with alcoholic cirrhosis nearly double that of patients with non-alcohol related cirrhosis. With roughly 60% of all patients with alcoholic cirrhosis being known to their GPs as alcoholics before the date of diagnosis of cirrhosis this may provide an opportunity for intervention(s) leading to behaviour and risk modification.

5 Progression of disease in people with cirrhosis

5.1 Introduction

This study aims to describe the progression of people with a diagnosis of cirrhosis based on clinical symptoms.

5.2 Methods

5.2.1 Dataset used

Data on all cases with cirrhosis (as described in section 2.4.3) were used in this analysis. Both subjects with incident and prevalent cirrhosis (as described in section 3.2.2.1), were included in this analysis. Subjects with no follow-up time were subsequently excluded from this analysis.

5.2.2 Additional definitions

5.2.2.1 Stages of disease

Within the population of cases with cirrhosis it was necessary for this study to define different stages or status of disease. I utilised the stages of cirrhosis as agreed at the Baveno IV consensus conference.[94] Each of these four stages is defined by the presence or absence of certain clinical symptoms:

Stage 1 – cirrhosis, no oesophageal varices, no ascites

Stage 2 – cirrhosis with oesophageal varices, no ascites, no bleeding

Stage 3 – cirrhosis with ascites with or without oesophageal varices

Stage 4 – cirrhosis with GI bleeding with or without ascites

Code lists were therefore constructed to represent ascites (Table 5-1) and any GI bleeding (see Table 5-2). The original code list for oesophageal varices

(see Table 2-2) was split into 2 separate lists – one representing non-bleeding oesophageal varices to represent stage 2 (see Table 5-3) and the second for bleeding oesophageal varices (see Table 5-4). These codes for bleeding oesophageal varices are also found in the code list for any GI bleeding.

Table 5-1 Medical codes for ascites (stage 3)

Description	medcode
[D]ASCITES	R095.00
[D]ASCITES NOS	R095z00
[D]FLUID IN PERITONEAL CAVITY	R095000
ASCITES (ABDOMINAL)	7853
CHYLOUS ASCITES	457 CA
CHYLOUS ASCITES	G86y100
DRAINAGE OF ASCITES NEC	7H2B200
HEPATIC ASCITES	5719AH
INSERTION OF DENVER PERITONEOVENOUS SHUNT	7H2B111
INSERTION OF LE VEEN PERITONEOVENOUS SHUNT	7H2B112
INSERTION OF PERITONEAL TO VENOUS SHUNT FOR ASCITES	7H2B113
O/E - ASCITES	25O..00
O/E - ASCITES - DIPPING SHOWN	25O2.00
O/E - ASCITES NOS	25OZ.00
O/E -ASCITES-SHIFTING DULLNESS	25O4.00
O/E-ASCITES-FLUID THRILL SHOWN	25O3.00
PARACENTESIS ABDOMINIS FOR ASCITES	7H2B000
PERITONEAL TO VENOUS DRAINAGE FOR ASCITES	7H2B100

Table 5-2 Medical codes for GI bleed (stage 4)

Description	medcode
ACUTE GASTRIC ULCER WITH HAEMORRHAGE	J110100
ACUTE GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	J110300
BLEEDING ACUTE GASTRIC ULCER	J110111
BLEEDING CHRONIC DUODENAL ULCER	J121111
BLEEDING CHRONIC GASTRIC ULCER	J111111
CHRONIC DUODENAL ULCER WITH HAEMORRHAGE	J121100
CHRONIC DUODENAL ULCER WITH HAEMORRHAGE AND PERFORATION	J121300
CHRONIC GASTRIC ULCER WITH HAEMORRHAGE	J111100
CHRONIC GASTRIC ULCER WITH HAEMORRHAGE AND PERFORATION	J111300
GASTROINTESTINAL HAEMORRHAGE UNSPECIFIED	J68z.00
GASTROTOMY AND LIGATION OF BLEEDING POINT OF STOMACH	7619100
GI BLEEDING	569 M
GIB - GASTROINTESTINAL BLEEDING	J68z.11
HAEMATEMESIS	J680.00
HAEMORRHAGE GASTROINTESTINAL	569 MI
INTESTINAL HAEMORRHAGE	569 MH
MELAENA	J681.00
OESOPHAGEAL VARICES WITH BLEEDING	G850.00
OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	G852000
OESOPHAGUS BLEEDING	5309H
OESOPHAGUS HAEMORRHAGE	5309HA
TANNER DEVASCULARISATION FOR BLEEDING VARICES	7609y11
UPPER GASTROINTESTINAL HAEMORRHAGE	569 ME
VOMITING OF BLOOD	J680.11

Table 5-3 Code list for non-bleeding oesophageal varices (stage 2)

Description	medcode
[X]OESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE	Gyu9400
FIBREOPTIC ENDOSCOPIC BANDING OF OESOPHAGEAL VARICES	760C500
FIBREOPTIC ENDOSCOPIC INJECTION SCLEROTHERAPY OESOPH VARICES	760C300
FUND HOLDING OP OESOPHAGEAL VARICES	K298 FH
GASTRIC VARICES	G857.00
INJECTION OESOPHAGEAL VARICES	K2982
LIGATION OESOPHAGEAL VARICES	K2981
LOCAL LIGATION OF OESOPHAGEAL VARICES	7609300
OESOPHAGEAL VARICES	G85..11
OESOPHAGEAL VARICES IN DISEASES EC	G852.00
OESOPHAGEAL VARICES IN DISEASES EC NOS	G852z00
OESOPHAGEAL VARICES NOS	G858.00
OESOPHAGEAL VARICES WITHOUT BLEEDING	G851.00
OESOPHAGEAL VARICES WITHOUT BLEEDING IN DISEASES EC	G852100
OPEN INJECTION SCLEROTHERAPY TO OESOPHAGEAL VARICES	7609400
OPEN OPERATION ON OESOPHAGEAL VARICES NOS	7609z00
OPEN OPERATIONS ON OESOPHAGEAL VARICES	7609
OTHER SPECIFIED OPEN OPERATION ON OESOPHAGEAL VARICES	7609y00
RIGID OESOPHAGOSCOPIC BANDING OF OESOPHAGEAL VARICES	760F400
RIGID OESOPHAGOSCOPIC INJECTION SCLEROTHERAPY OESOPH VARICES	760F300
VARIX OESOPHAGUS	4560

Table 5-4 Code list for bleeding oesophageal varices

Description	medcode
OESOPHAGEAL VARICES WITH BLEEDING	G850.00
OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	G852000
TANNER DEVASCULARISATION FOR BLEEDING VARICES	7609y11

I assigned a date of entry to each stage as the earliest date of any recorded code contained within each stage including data collected in the pre-UTS period. Cases were then assigned a stage of entry into the study as the earliest of these 4 stages. Due to the nature of the original extraction of cases with cirrhosis (including therapeutic or diagnostic codes for oesophageal varices and codes for portal hypertension) it was possible for a case to enter this study at a stage later than stage 1. It was also possible for a case to have a code for an early stage subsequent to a code for a later stage. For example, if a case had a code for stage 1 subsequent to a code for stage 3 the case would be assigned an entry stage as stage 3 and would not be included in stage 1 or 2 at any point in the analysis.
Compensated cirrhosis was then defined as patients when in either of stages 1 and 2 with decompensated cirrhosis as stages 3 and 4.

To minimise the potential for misclassification of patients with decompensated cirrhosis as patients with compensated disease I additionally looked for recording of one or more prescriptions for spironolactone as evidence for decompensation.

5.2.3 Statistical analysis

I examined the probabilities of patients with cirrhosis progressing from an individual stage to a subsequent stage or death within one year and state progressions across the whole time period of their records. 95% CIs were calculated using the binomial distribution. I calculated the proportion of GI bleed that was coded as oesophageal bleeding.

As mortality was seen to vary substantially by presumed aetiology (see section 4.3.2.4) I also then stratified the cohort into those with alcoholic cirrhosis and those with non-alcohol related cirrhosis.

Using Cox proportional hazards I modelled the rate of decompensation in the group of patients with compensated disease. Subjects entered the analysis period at the date of earliest recorded code for stage 1 or 2 and exited at the earliest of either date of earliest recorded code for stage 3 or 4, date of death, date of deregistration with their general practice or 30 April 2002 which was the last date of available data in this dataset. Again, I examined progression for subjects with alcoholic cirrhosis and those with non-alcohol related cirrhosis. Follow-up time was split at 1 year and I modelled the rate of decompensation during the first year after diagnosis and subsequent to that first year again stratifying by presumed aetiology.

5.3 Results

Of the 4,537 patients identified with cirrhosis, 66.0% entered the study cohort at stage 1, 14.6% at stage 2, 10.5% at stage 3 and 8.8% at stage 4.
Of the 877 patients considered decompensated at entry 71% had evidence of spironolactone use at any point in their record compared with 43% of subjects considered compensated (at entry). Of the 3660 patients considered compensated at entry, 505 (13.8%) had evidence of a prescription of spironolactone occurring before a recording of decompensation within their GPRD record. Of the patients with a record of GI bleed at any point in their record, for only 7.4% of these patients was this specified as oesophageal bleeding.

Outcome probabilities in the first year are shown in Figure 5-1. Patients in stage 1 and 2, i.e. compensated cirrhosis, had a one-year probability of proceeding directly to death of just over 10%. The mortality in patients in stage 3 and 4, i.e. decompensated cirrhosis, was much higher with 25.9% and 18.2% respectively of patients proceeding directly to death.
State progressions across the whole study period are shown in Figure 5-2. Of note is the high proportion of people in the early stages of disease i.e. patients with compensated cirrhosis, who progressed directly to death without the recording of other clinical symptoms of decompensation.

The probability of progressing both during the first year and state progressions subsequently for those with alcoholic cirrhosis and non alcohol-related cirrhosis are shown in Table 5-5 and Table 5-6 respectively. Reading across the table shows the stage at which patients began their follow-up. The rows in the column represent the stage to which the patients directly progressed. For

example looking at the first column we can see that alcoholics who began follow-up in stage 1 had a 74.4% chance of remaining in stage 1 during the first year, with 4.0% progressing directly to stage 2 (oesophageal varices), and so on. In the first year following diagnosis patients with alcoholic cirrhosis had a slightly higher probability of progressing to another stage of cirrhosis than those with non-alcohol related cirrhosis but a lower probability of progressing directly to death. Across the whole study period patients with a presumed aetiology of alcoholic cirrhosis were again more likely to progress to another later stage of cirrhosis than those with non-alcohol related cirrhosis. The differences in progression directly to death were not so marked across the whole time period, rather less patients with alcoholic cirrhosis remained in their entry stage with the exception of patients in stage 3.

Overall, the rate of decompensation for those patients with compensated disease was 5.5% per year (95%CI[5.1%, 5.9%]). As might be expected (following the results in Chapter 4 and those reported above) this figure varied considerably both by length of follow-up and by presumed aetiology.
During the first year after diagnosis the rate of decompensation for those patients with a presumed aetiology of alcoholic cirrhosis was 16% (95%CI [14.1%, 18.3%]) compared with only 9.7% (95%CI [8.2%, 11.4%] for those with non-alcohol related cirrhosis.
Following the first year the rate of decompensation did not vary much by presumed aetiology with a rate of 3.8% per year (95%CI [3.3%, 4.4%)] for those with alcoholic cirrhosis compared with a rate of decompensation of 3.0% per year (95%CI [2.6%, 3.6%]) for those with non-alcohol related cirrhosis.

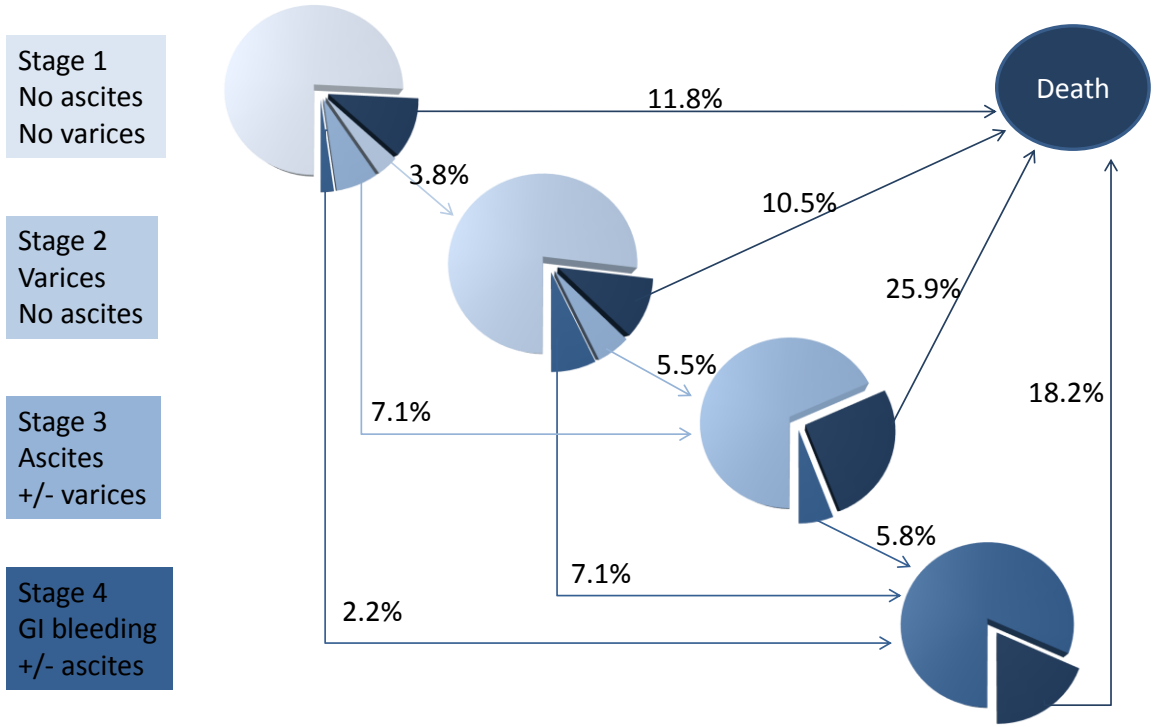


Figure 5-1 Probabilities for progression within one year, all patients

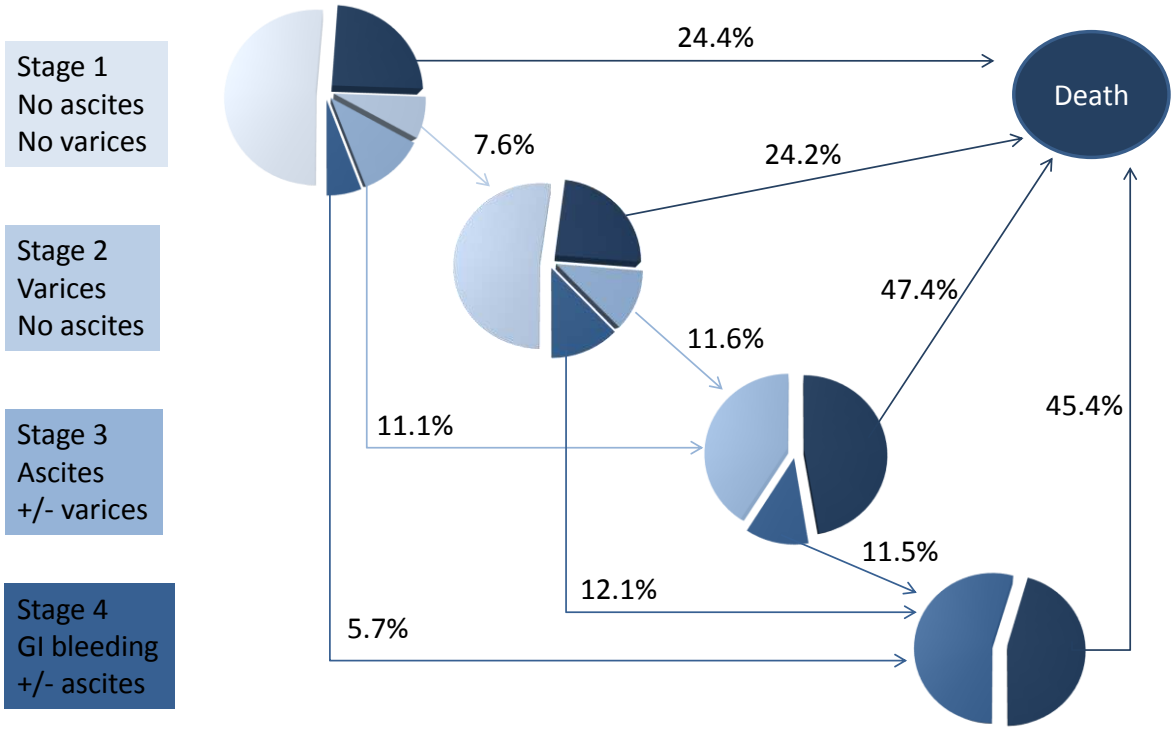


Figure 5-2 State progression across whole record, all patients

Table 5-5 Probability of progression in first year, patients with alcoholic and non-alcohol related cirrhosis

		Stage from							
		Stage 1		Stage 2		Stage 3		Stage 4	
		Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related
Progression directly to / remained in	Stage 1	74.4 [72.2, 76.5]	77.4 [75.1, 79.5]	-	-	-	-	-	-
	Stage 2	4.0 [3.1, 5.1]	3.6 [2.7, 4.7]	74.0 [69.0, 78.6]	78.8 [75.1, 82.2]	-	-	-	-
	Stage 3	8.6 [7.2, 10.1]	5.5 [4.4, 6.9]	6.2 [3.9, 9.3]	5.0 [3.3, 7.2]	72.7 [68.8, 76.4]	61.7 [56.5, 66.7]	-	-
	Stage 4	3.2 [2.3, 4.1]	1.1 [0.7, 1.8]	9.4 [6.5, 13.1]	5.6 [3.8, 7.9]	7.0 [5.0, 9.4]	4.1 [2.3, 6.6]	83.5 [79.5, 86.9]	79.6 [74.8, 83.8]
	Death	9.9 [8.5, 11.5]	12.3 [10.7, 14.2]	10.3 [7.3, 14.1]	10.6 [8.1, 13.5]	20.3 [17.0, 24.0]	34.2 [29.4, 39.3]	16.5 [13.1, 20.5]	20.4 [16.2, 25.2]

Table 5-6 State progression across whole record, patients with alcoholic and non-alcohol related cirrhosis

		Stage from							
		Stage 1		Stage 2		Stage 3		Stage 4	
		Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related	Alcoholic	Non-alcohol related
Progression directly to / remained in	Stage 1	47.4 [44.9, 49.9]	55.4 [52.8, 58.0]	-	-	-	-	-	-
	Stage 2	8.1 [6.8, 9.5]	7.1 [5.8, 8.6]	47.2 [41.8, 52.7]	55.2 [50.9, 59.5]	-	-	-	-
	Stage 3	13.2 [11.6, 15.0]	8.8 [7.4, 10.4]	13.6 [10.1, 17.7	10.4 [8.0, 13.3]	45.2 [41.0, 49.5]	35.1 [30.2, 40.2]	-	-
	Stage 4	6.8 [5.6, 8.2]	4.4 [3.4, 5.6]	15.3 [11.7, 19.6]	10.0 [7.6, 12.9]	13.2 [10.5, 16.3]	9.0 [6.3, 12.4]	54.7 [49.8, 59.5]	54.5 [48.9, 60.0]
	Death	24.5 [22.4, 26.7]	24.3 [22.1, 26.6]	23.9 [19.35, 28.8]	24.3 [20.8, 28.2]	41.6 [37.4, 45.8]	56.0 [50.7, 61.1]	45.3 [40.5, 50.2]	45.5 [40.0, 51.1]

5.4 Discussion

5.4.1 Key findings

Using the clinical observations recorded in the primary care records of people with cirrhosis I have described the progression of disease as experienced by patients and as recorded by primary care physicians in the UK. The presence of ascites rather than GI bleed appears to represent a more serious marker of mortality within the first year following diagnosis.

Overall the rate of decompensation was 5.5% per year (95%CI[5.1%, 5.9%]). The rate of decompensation varied considerably by presumed aetiology of cirrhosis with alcoholic cirrhosis conferring a worse prognosis in the first year following diagnosis (16% versus 10%). These differences were largely removed following this first year and the rate of decompensation was approximately 3-4% per year for all patients.

5.4.2 Strengths and limitations

This study has tried to utilise a recognised staging system of cirrhosis and apply its definitions to a cohort of patients whose data are recorded in primary care. The usefulness of a staging system such as this, particularly one with no reliance on laboratory measurements, allows for a simpler identification of patients at a higher risk of progression and/or mortality and the easier communication of this risk to patients and their families.

This study is three times the size of that of the previous study upon which the Baveno IV consensus stages were derived and on which I have based my methodology. The inclusion of patients who did not necessarily have to be hospitalised in this study means that the results are perhaps more relevant to

those ambulatory patients, as would be being seen in primary care and outpatients clinics, than previously available figures. By virtue of the size of this study it was possible to stratify the probabilities of progression by presumed aetiology.

The principal limitation with this study, similar to that with the previous two studies, is that of the diagnosis and recording of the symptoms of cirrhosis that define the staging. The cost of requesting records of patients within each stage means that I was unable to validate the specific stages of cirrhosis in this cohort. Within the GPRD itself there is insufficient data to assess what level of follow-up was being performed for an individual patient. It is probable that many patients in stage 1 were not undergoing regular screening endoscopies for the presence of oesophageal varices and so the probability of progressing from stage 1 to stage 2 is therefore underestimated with oesophageal varices perhaps only being recorded if they had led to a bleed. Similarly it is possible that only more severe bleeds are being recorded if a patient was not undergoing regular screening endoscopies. It is additionally possible that those patients who died in hospital following bleeding oesophageal varices (or indeed any other sort of GI bleed) had the fact of death communicated to the GP but not the circumstances leading up to it. For this reason it is possible that the progression to stage 4, and the probability of proceeding from stage 4 to death is underestimated within these data. These limitations in the validity of the staging system could also lead to an overestimate in the progression directly to death for earlier stages. However, I would argue that the figures I have reported represent the 'real-life' situation of what is identified and communicated regardless of the variation in the follow-up of patients that may exist in different regions or indeed individual hospitals. These figures are therefore a useful adjunct to other available data for the

communication of risk to patients in both the primary care and outpatient settings.

I was not able to calculate other more commonly used measures of severity of disease such as the Child-Pugh score or MELD score as the blood indices required for the calculation of these scores were not available in the data. There are however limitations in these scores, particularly the speed with which it is possible to calculate a Child-Pugh or MELD score and the day-to-day clinically observed variations in blood measurements that may cause a significant change in the scores (particularly with respect to creatinine and prothrombin time). These scores are also more difficult to communicate in a meaningful way to most patients where the presence or absence of clinical symptoms is likely to be more readily understood. Indeed a considerable wealth of literature exists suggesting that rather than a measure of individual risk patients are more likely to comprehend figures which are described in terms of the proportions of patients likely to experience an outcome.[95] These sorts of figures can easily be extracted from the results reported above e.g. if a patient has been diagnosed with alcoholic cirrhosis in stage 1 it would be possible to communicate to that patient 'In the first year following diagnosis with alcoholic cirrhosis, such as yourself, 3 in 4 patients will remain in this disease stage and not experience any further sequelae. The other 1 in 4 patients will experience some further symptoms including varices, ascites, bleeding and 1 in 10 may even die within a year' or similar.

With respect to the presumed aetiology of cirrhosis there are potential limitations in the methods I have employed to assign the cause of cirrhosis as described in section 3.4.2. The likelihood of misclassifying patients with alcoholic cirrhosis as non-alcohol related cirrhosis could lead to an

underestimate of the true progression associated with an aetiology of alcoholic cirrhosis and a corresponding overestimate of the progression associated with non-alcohol related cirrhosis. Again, owing to the relatively small number of patients with other known aetiologies (viral hepatitis, autoimmune liver disease or metabolic liver disease) it was not possible to describe the progression of these patients with precision.

5.4.3 Comparison with previously published work

In this study I have attempted to replicate a staging system for cirrhosis adopted at the Baveno IV consensus conference.[94] These stages are based on data from a single hospital in Sicily in the 1970s and 1980s, published as one paper and one abstract.[44 96] The two studies were aggregated and the 1-year outcome probabilities were published in a systematic review looking at prognostic indicators of survival in cirrhosis.[55] The methods for calculating the 1-year outcome probabilities are uncertain as there are no methods included in this latter paper. Going back to the original paper and the abstract, 1-year outcome probabilities for the occurrence of oesophageal varices were calculated as cumulative 10-year progression divided by 10 to get the annual progression, with the methods for progression to other states not clarified. Progression is not necessarily uniform across time, particularly not within the first year as I have demonstrated with my data, and as such the validity of these widely referenced figures is somewhat questionable.

Bearing in mind the limitations of the description of the methods employed to calculate data, the 1-year progression probabilities described by D'Amico and colleagues are the most logical comparison for my results and are displayed in Table 5-7.

Table 5-7 Probability of progression in cirrhosis
as reported in D'Amico G, Garcia-Tsao G, Pagliaro L. 'Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies' J Hepatol (2006)44(1):217-231

		Progression from			
		Stage1	**Stage 2**	**Stage 3**	**Stage 4**
Progression to	**Stage 1**	88.6%	-	-	-
	Stage 2	7%	86%	-	-
	Stage 3	4.4%	6.6%	72.4%	-
	Stage 4	0%	4%	7.6%	43%
	Death	1%	3.4%	20%	57%

In terms of mortality my results show a much higher progression to death from both stage 1 and stage 2 but a very much lower progression to death from stage 4. Aside from the possible methodological considerations there are probably two principal reasons for these observed differences. Firstly, as described above it is possible that without regular follow-up there is misclassification of patients as stage 1 when in fact they have already reached a later stage, but that this has not been diagnosed or has not been reported back to primary care and therefore is not recorded in the GPRD. However, as we do not know the exact methods of follow-up in the Sicilian population (the abstract references patients undergoing 'endoscopy at 1-3 year intervals or at bleeding')[96] it is not conclusive that it is difference in follow-up that would have led to these differences in reported survival. Secondly, it is possible that the composition of the cirrhosis cohorts in this earlier study and in my study have significant differences in aetiology. Indeed the population of Sicily has a much higher prevalence of hepatitis than I have reported in my data. Given that patients with alcoholic cirrhosis appear to have a worse prognosis (as seen from my data) it is possible that this discrepancy in survival for compensated patients is a reflection of the large proportion of alcoholic cirrhosis within the UK population who fare worse than those with an aetiology of non-alcohol related cirrhosis.

The observation that the presence of ascites rather than GI bleed seems to confer a greater risk of mortality within the first year is in contrast to those data from Sicily. However, given that the main period of data collection is some 20 years later, it is probable that the patients included in my study have had available to them many of the clinical improvements in the management of variceal bleeding that were not likewise available for those people in the earlier study. These improvements include endoscopic sclerotherapy, endoscopic ligation, medications such as vasopressin, somatostatin and octreotide, all of which are likely to have been available during the period of my study but not for the patients in the study in Sicily.[97] Indeed, three relatively recent papers from the USA, France and Sweden report improved survival after oesophageal variceal bleeding.[58 59 60] However, the overall mortality from GI bleeding in my data is still lower than the 579 days median survival reported in the US for patients hospitalized with an oesophageal bleed in 1988-91,[58] or the 1-year mortality of over 50% reported in Sweden for patients discharged between 1990-2002 after a diagnosis of oesophageal varices.[60] Gastrointestinal bleeding is multi-factorial and it is possible that the bleeding I have identified and included in my study is not as severe as the bleeding reported in these previous studies. Indeed only 7.4% of the bleeding identified was recorded as variceal in origin.

The 1-year probability of progression from stage 1 to stage 2 of 3.8% though similar to that seen in some studies describing the yearly 'incidence' of varices[98 99] is lower than that reported in most studies looking at the natural history of cirrhosis including the study from Sicily. [55 100 101 102] This is quite likely to be due to the fact that we do not know what, if any, level of endoscopic surveillance was being undertaken on these patients. There was

no definitive screening guideline in place in the UK at the time of data collection and as such I will likely have an underestimate of the progression from stage 1 to stage 2 (as discussed in section 5.4.2). However, if I include the 2.2% of patients who progressed directly from stage 1 to stage 4 i.e. identification of bleeding without prior identification of varices, assuming all these bleeds were of variceal origin, the progression to varices becomes quite similar, at 6%. Inevitably, in the absence of routine screening endoscopies, some varices will be identified only if they bleed.

The 1-year progression to stage 3 from either stage 1 or stage 2 (cumulative progression 12.6%) was similar to the 11% observed by D'Amico and colleagues. [55] Studies looking at populations with a high proportion of viral cirrhosis report variable rates of progression to ascites with 5-year incidence of only 11%[103] and 24.8%.[101] The study by Benvegnu et al. showed that alcohol abuse was associated with a higher incidence of ascites compared with those with no history of alcohol abuse.[103] Overall progression to ascites in my study with over half of the study population having a presumed aetiology of alcoholic cirrhosis was 22.7%. Progression to ascites was higher in those with alcoholic cirrhosis than those with non-alcohol related cirrhosis both within the first year and throughout the study period.

Progression to stage 4 (GI bleeding) within the first year following diagnosis is slightly higher in my study than that reported by D'Amico and colleagues[55] but is consistent with the 24% bleeding rate at 2 years from two earlier studies.[104] [105]

It is possible to compare the prognosis figures for patients with alcoholic cirrhosis directly to a study conducted in Denmark and reported in 2009.[56]

The authors report on 449 patients with alcoholic cirrhosis diagnosed and followed up between 1993 and 2005 in a single hospital centre. The 1-year progression directly to death in this hospital was 10% for those with no reported complications, almost identical to the 9.9% I saw in my study. The 1-year progression directly to death for patients with clinical symptoms of ascites and variceal bleeding was 15% and 11% respectively, slightly lower than the figures I reported for stage 3 and stage 4 (20.3% and 16.5%) although the confidence intervals around these point estimates do overlap. Perhaps unsurprisingly, this study reported that the complications of cirrhosis do not develop in such a well-determined order as put forward by the staging system I have tried to replicate with ascites reported as the most frequent first complication (in 12% of patients) but nearly as many (10% in total) developing variceal bleeding (6%) or hepatic encephalopathy (4%) as their first complication. There are no such comparable figures for patients with non-alcohol related cirrhosis although the work from D'Amico and colleagues is probably more likely to reflect non-alcohol related cirrhosis given the high proportion of hepatitis in that population.[55]

5.4.4 Conclusions

This study has described the clinical progression following a diagnosis of cirrhosis as recorded in contemporary clinical practice in primary care. The figures based on this relatively simplistic staging system are potentially more relevant and readily understood by those living with cirrhosis and those communicating risk to these patients.

This study is the first (to my knowledge) to describe the rate of decompensation in patients with compensated disease stratified by aetiology and shows a significantly higher rate of decompensation for those with alcoholic cirrhosis in the first year compared to those with non-alcohol related cirrhosis. These figures will be of use to service providers to factor in the aetiology of cirrhosis in the planning of therapies, interventions and follow-up as well as to individual clinicians and their patients to enable a clearer understanding of the likely clinical course of this disease.

6 The "MRC Elderly" Database

This chapter provides an overview of the "MRC Elderly" database, its data format, its strengths and weaknesses particularly with reference to the studies in chapters 7 through 9 and details regarding the data used for studies contained within these three chapters. Additional study-specific information on the exact data used is detailed in the methods section of each individual chapter.

6.1 Original data collection

These studies utilise data collected as part of the Medical Research Council (MRC) Trial of Assessment and Management of Older People in the Community which has been reported on previously.[106 107 108] Briefly, practices within the MRC General Practice Research Framework with list sizes of between 200 and 700 patients aged 75 and over, selected to represent the population of the UK based on mortality (SMRs) and deprivation (Jarman score), were eligible to be randomised into the trial. In total, 109 practices were invited to participate in the trial and a final total of 106 practices provided data.

All people aged 75 or over registered with the selected general practices, non-resident in nursing homes, and who were not known to be terminally ill, were eligible for inclusion in the data collection which comprised two arms comparing multi-dimensional assessment of the elderly. The first arm (universal arm) invited all patients to an in-depth health assessment whilst the second arm (targeted arm) invited only selected patients.

Recruitment and data collection took place between 1995 and 1999. Local Research Ethics Committee approvals were obtained for each participating practice.

All participants in the original trial received a brief assessment of health covering all areas included within the GP contract[109] with data collected either at interview with a lay person, at interview by a study nurse or by postal questionnaire (see Figure 6-1). Following this brief assessment subjects in the universal arm of the trial had a detailed nurse assessment covering these same areas but in more detail. Additional biological measurements were made, including blood pressure and heart rate, and participants had a blood sample taken for a biochemical screen including measurements of serum aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin. The studies described in chapters 7-9 utilise data collected from participants within the universal arm of the trial only.

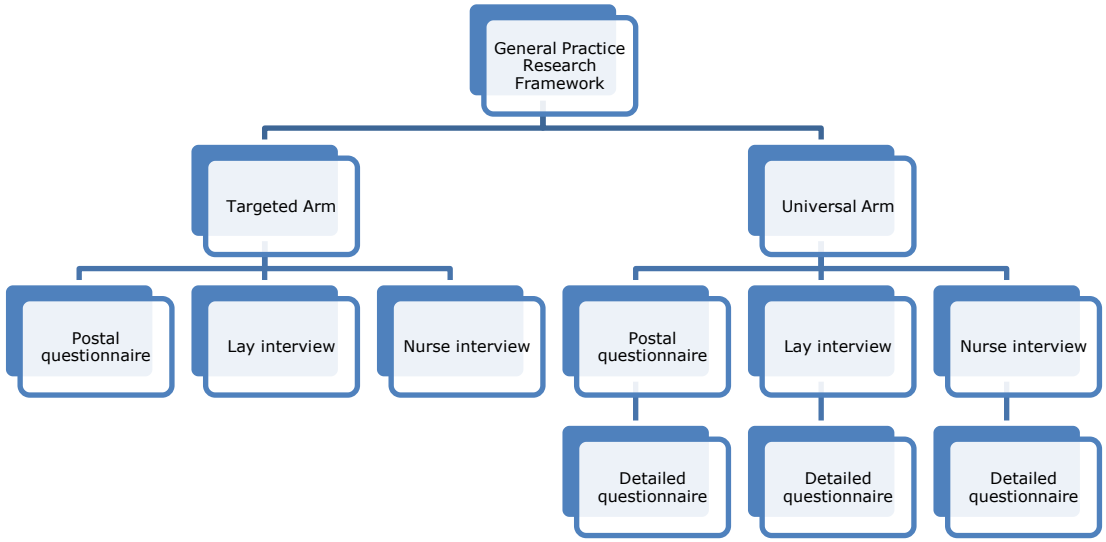


Figure 6-1 Design of the MRC trial of assessment and management of older people in the community

6.2 Data flow

Data flow was initiated following the recruitment of participants from general practices registered as part of the MRC General Practice Research Framework. All participants then had information recorded from the brief assessment questionnaires stored in the 'brief' database. All data collected during the detailed assessment were stored in the 'detail' database.

All participants in the trial were registered with the NHS central register (NHSCR) and listings of events including death, embarkation, registration with the armed services, 'cancellations' (when a patient can no longer be contacted at a particular general practice the NHSCR will mark the record as 'cancelled' until such time as the patient transfers to another GP or a death occurs and can be traced to that individual) and re-entries were received on a monthly basis. All 'non-death' events were stored in the 'censoring' database. Death certificates were also received on a monthly basis with coded cause of death and date of death recorded in the 'deaths' database.

A schematic diagram of the data flows is shown in Figure 6-2.

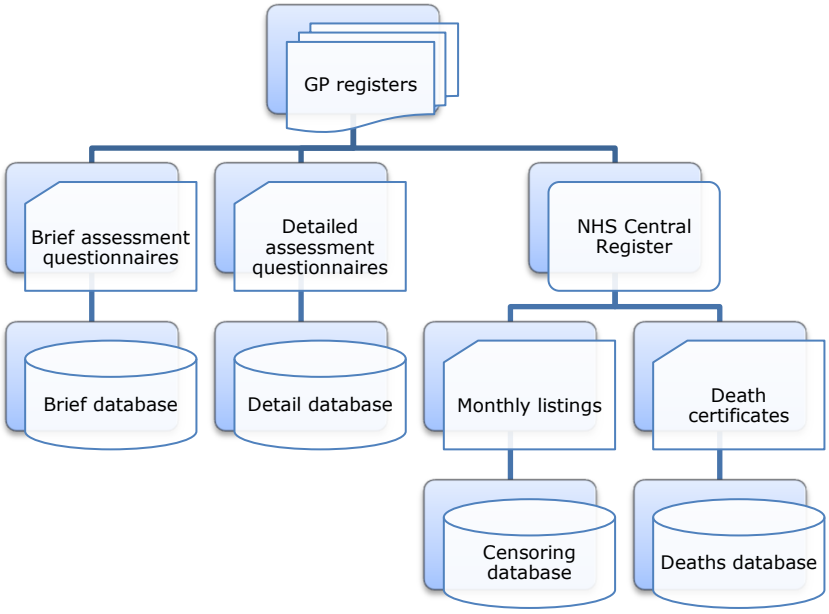


Figure 6-2 Data repositories and information flow in the MRC elderly study

6.3 Strength and weaknesses

The “MRC Elderly” is a useful resource for descriptive epidemiology and has recently been utilised to describe kidney disease in older people.[110] However, as with any database there are limitations to its usefulness which should be considered. The relative merits and limitations of the “MRC Elderly” database, particularly with reference to studies of liver function, are discussed below.

6.3.1 Representative

The cluster randomised nature of the initial study means that participants included in the universal arm of the trial (and therefore the subjects in my following studies) were chosen in a way which is representative of the population of the UK with respect to mortality and deprivation. The subsequent exclusion of patients who were in long-term care or those with terminal illness should mean that the results of these subsequent studies can be generalised to the ambulatory, non-terminally ill population of the UK aged 75 and over.

6.3.2 Availability of data on liver function tests

All participants in the universal arm had a blood sample taken with several biochemical markers examined including three markers commonly used in the assessment of liver function, namely serum aspartate transaminase (AST), alkaline phosphatase (ALP) and bilirubin. As these data are being used as a secondary source and there was no opportunity for further data collection from the participants there are certain data items that are not available that would have been desirable if setting up this study specifically to look at liver function

tests. These include particular biochemistry markers e.g. alanine aminotransferase, INR or pro-thrombin time, and also potential confounders such as the diagnosis of recognised liver disease.

6.3.3 Follow-up

Follow-up of the "MRC Elderly" cohort for the principal event of interest of death was well executed through the flagging with the NHSCR and continues to be updated. At the time of data extraction for these studies death data were available up until 5 November 2005. With death being a common event in a population of people aged 75 and over this gives the study good power to examine the association between elevated liver function tests with mortality.

6.4 Data used for chapters 7-9

For the purposes of the following studies I obtained data on those subjects from 53/106 general practices which comprised the universal arm. This included all of the information from the detailed nurse interview, including blood test results, and separate data files from the NHSCR giving information on the subjects within the study who had subsequently died or migrated. Details on the exact data used for each study are described in the appropriate chapter.

7 Prevalence of elevated liver function tests in the elderly

7.1 Introduction

This study aims to estimate the prevalence of elevated liver function tests in a sample of people aged 75 and over resident in the UK.

7.2 Methods

7.2.1 Data set used

The data used in this study are those from the detailed nurse assessment contained within the 'detail' database (see Figure 6-2). A total of 15,308 participants aged 75 and over are included in the subsequent analyses.

7.2.2 Imputation of laboratory reference ranges

In order to assess the prevalence of elevated liver function it is necessary to have an agreed cut off limit or definition for abnormality. However, there was no standard definition of abnormality in use at the time of data collection for any of the three tests that I was interested in. Different laboratories used different assays and these were calibrated individually and hence had different designated limits of normality. In addition, reference ranges were frequently set at different levels for males and for females.

Reference ranges for the upper and lower limits of normal tests were not collected at the time of the study and, following requests after the completion of the study, only half of the practices involved had any recorded reference

ranges for the three liver function tests I was interested in. For those practices where I did not have a provided reference range it was therefore necessary to impute a sensible value to use as a cut off for limits of normality.

To do this I examined the distribution of the values of the upper and lower limits of normal for the laboratories which had provided reference ranges. Where the distribution of tests appeared to be unimodal I inferred that there was broadly one standard test in operation for the particular test. Where the distribution of tests appeared to be bimodal I inferred that there were two standard tests operating in parallel. This assumption was discussed with clinical colleagues using these tests throughout the time period of the data collection and was agreed to be representative of laboratory practices at that time. Practices were assigned to either the lower or upper test limit depending on the median value of test results from participants within that practice.

For those practices where information on reference ranges was provided these values were used. For practices without reference ranges I derived three sets of upper limits:

1. Upper limit based on the median values given for those practices for which information was already available.
2. Upper limit based on the minimum upper limit for those practices for which information was already available – this provides an estimate of the maximum number of abnormal test results.
3. Upper limit based on the maximum upper limit for those practices for which information was already available – this provides an estimate of the minimum number of abnormal test results.

7.2.2.1 AST

A total of 28/53 (53%) practices had some information recorded on AST reference ranges. All reference ranges provided were for adults of all ages. Some practices provided different reference ranges dependent on the sex of the patient. It was therefore necessary to impute value for upper limits for men and women for 25 practices without a given reference range. Graphical representation of the upper limits showed the distributions of the upper limits to be largely unimodal around 40IU/l for both males and females (see Figure 7-1 for males; same distribution seen for females (not shown)). Interrogation of the actual test results showed a similar unimodal distribution of the median values by practice (see Figure 7-2).

I therefore inferred that there was only one primary test in operation for AST among the practices included in the trial at the time these data were collected. Summary statistics on the distribution of given reference ranges can be seen in Table 7-1.

For practices without reference ranges the three sets of upper limits imputed were:

1. Based on the median values – 40IU/l for both males and females.
2. Based on the minimum upper limit – 31IU/l for males, 30IU/l for females.
3. Based on the maximum upper limit – 57IU/l for males, 53IU/l for females.

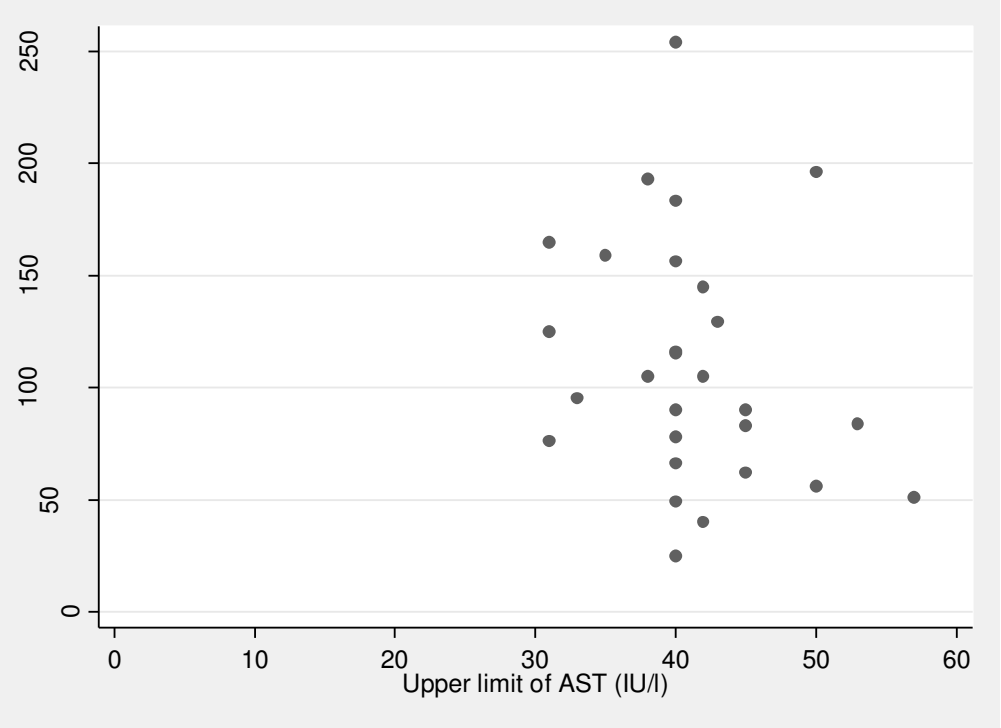


Figure 7-1 Graphical representation of upper limits of reference range for AST test by size of practice (males only)

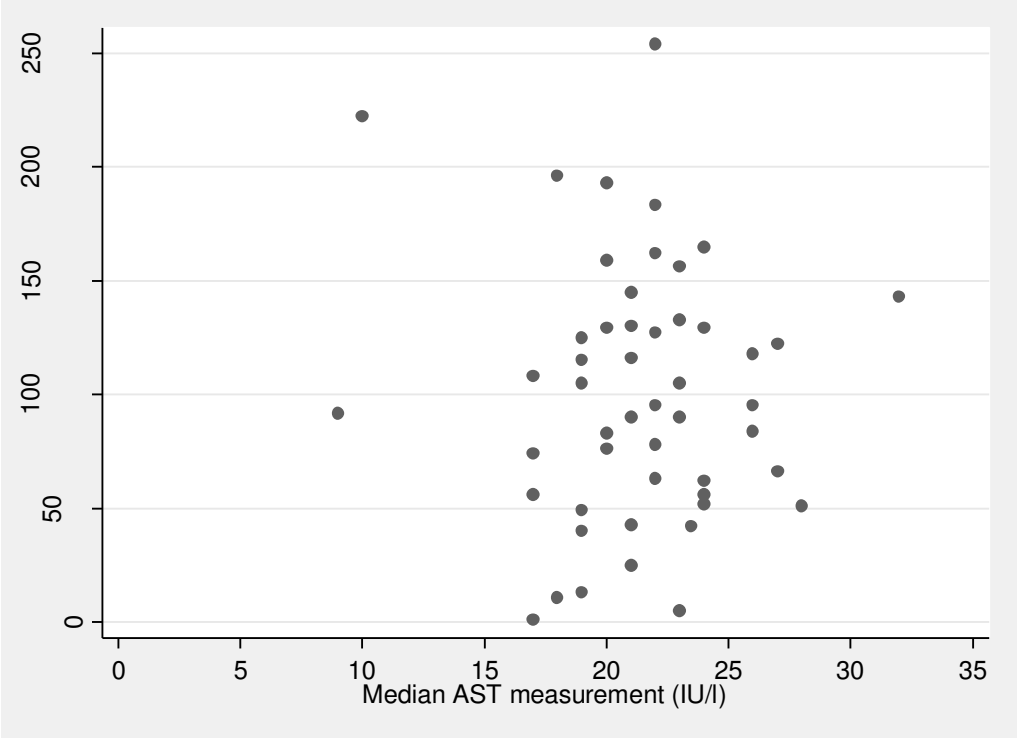


Figure 7-2 Graphical representation of median AST test measurements by size of practice (males only)

Table 7-1 Lower and upper limits of normal range of AST

		Number of practices	Median [IQR] (IU/l)	Range (IU/l)
Males	Lower limit	20	10 [0.5, 11]	0-20
	Upper limit	28	40 [39, 44]	31-57
Females	Lower limit	20	5 [0.5, 10]	0-15
	Upper limit	28	40 [35, 42]	30-53

7.2.2.2 ALP

A total of 28/53 (53%) practices had some information recorded on ALP reference ranges. Reference ranges provided were for adults of all ages or for adults aged 60 and over. Some practices provided different reference ranges dependent on the sex of the patient. It was therefore necessary to impute upper limits for 25 practices without a given reference range. Graphical representation of the upper limits showed the distributions to be bimodal with one peak at around 110IU/l and another at around 300IU/l for both males and females (see Figure 7-3 for males; same distribution for females (not shown)). Interrogation of actual test results showed a similar bimodal distribution of the median values by practice (see Figure 7-4). I therefore inferred that there were two primary tests in operation for ALP among the practices included in the trial at the time these data were collected. Practices without reference ranges were assigned to the lower or higher test based on the median of actual test results of the participants within the practice. Summary statistics on the distribution of given reference ranges for the lower and higher test can be seen in Table 7-2 and Table 7-3 respectively.

For practices without reference ranges the three sets of upper limits imputed were:

1. Based on the median values – 120IU/l for both males and females in lower test group; 330IU/l for both males and females in higher test group.
2. Based on the minimum upper limit – 50IU/l for both males and females in lower test group; 129IU/l for males and 104IU/l for females in higher test group.

3. Based on the maximum upper limit – 237IU/l for both males and females in lower test group; 350IU/l for both males and females in higher test group.

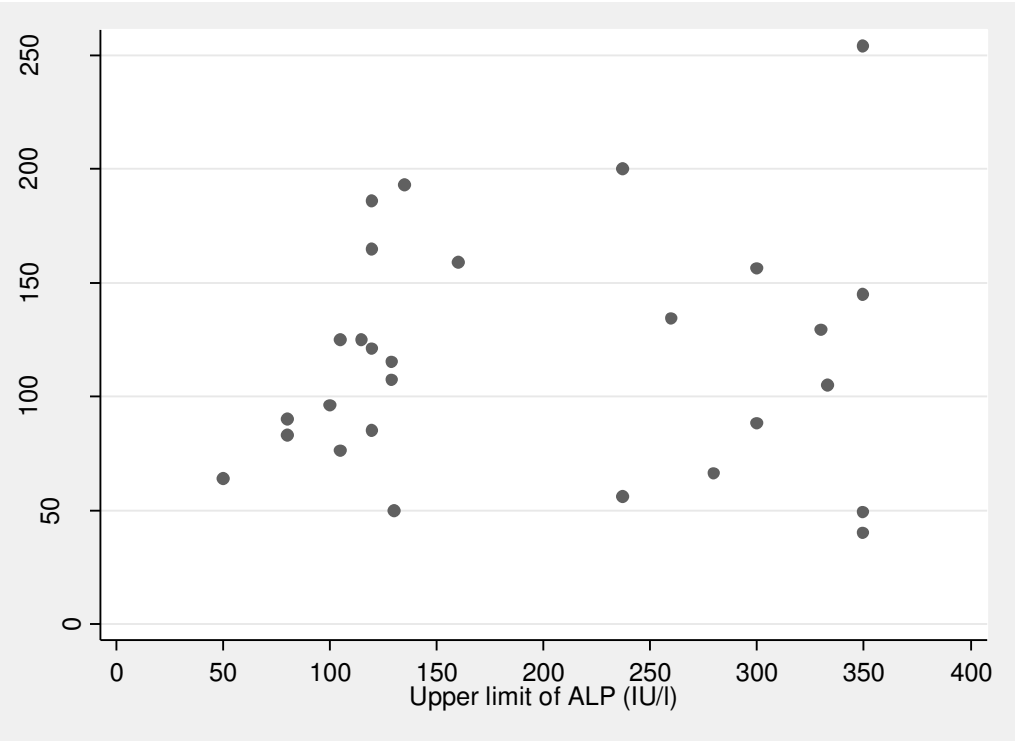


Figure 7-3 Graphical representation of upper limits of reference range for ALP test by size of practice (males only)

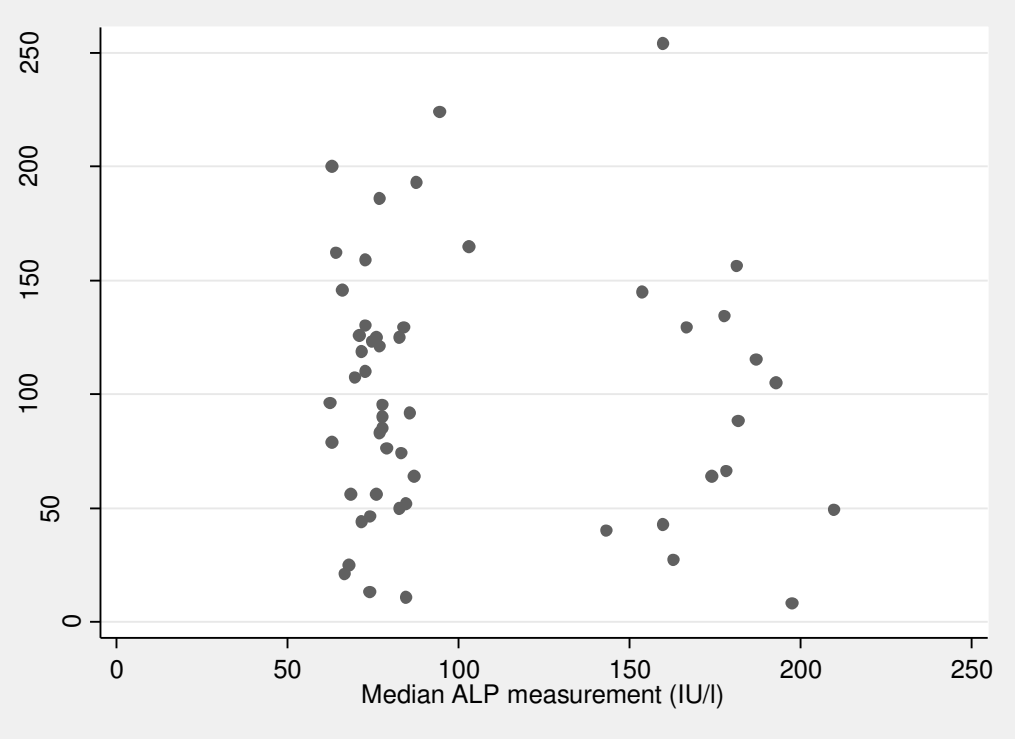


Figure 7-4 Graphical representation of median ALP test measurements by size of practice (males only)

Table 7-2 ALP Lower test – known reference ranges

		Number of practices	Median [IQR] (IU/l)	Range (IU/l)
Males	Lower limit	17	30 [25, 35]	0-40
	Upper limit	17	120 [105, 130]	50-237
Females	Lower limit	17	30 [25, 35]	0-40
	Upper limit	17	120 [105, 135]	50-237

Table 7-3 ALP Higher test – known reference ranges

		Number of practices	Median [IQR] (IU/l)	Range (IU/l)
Males	Lower limit	11	70 [0, 100]	0-100
	Upper limit	11	330 [280, 350]	129-350
Females	Lower limit	11	70 [0, 100]	0-100
	Upper limit	11	330 [280, 350]	104-350

7.2.2.3 Bilirubin

A total of 30/53 (57%) of practices had some information recorded on bilirubin reference ranges. Reference ranges provided were for adults of all ages. No practices provided different reference ranges dependent on the sex of the patient. It was therefore necessary to impute upper limits for 23 practices without a given reference range. Graphical representation of the upper limits showed the distribution to be unimodal around 17µmol/l (see Figure 7-5). Interrogation of actual test results showed a similar unimodal distribution of the median values by practice (see Figure 7-6). I therefore inferred that there was only one primary test in operation for bilirubin among the practices included in the trial at the time these data were collected. Summary statistics on the distribution of given reference ranges can be seen in Table 7-4.

For practices without reference ranges the three upper limits imputed were:

1. Based on the median values – 17µmol/l for both males and females.
2. Based on the minimum upper limit – 15µmol/l for both males and females.
3. Based on the maximum upper limit – 25µmol/l for both males and females.

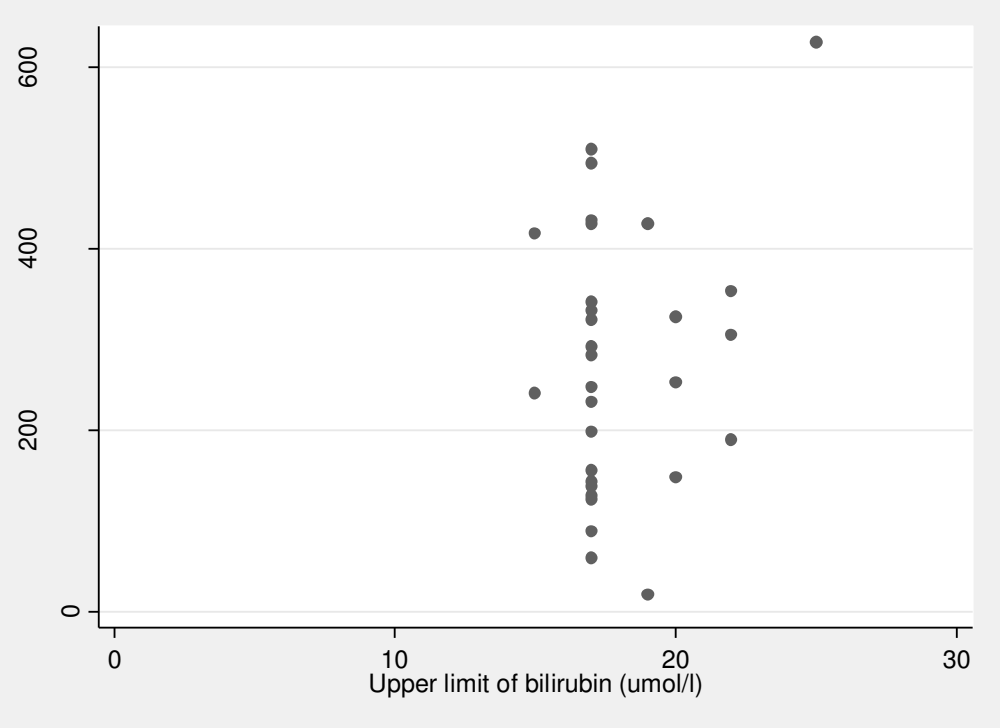


Figure 7-5 Graphical representation of upper limits of reference range for bilirubin test by size of practice

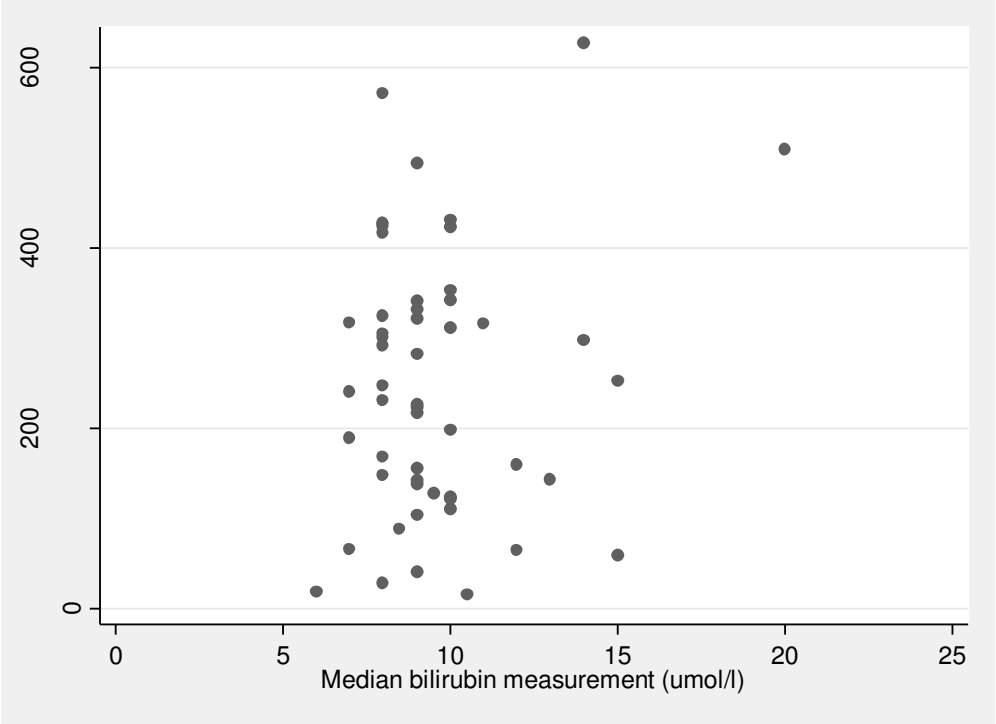


Figure 7-6 Graphical representation of median bilirubin test measurements by size of practice

Table 7-4 Bilirubin tests – known reference ranges

	Number of practices	Median [IQR] (µmol/l)	Range (µmol/l)
Lower limit	30	0 [0, 3]	0-5
Upper limit	30	17 [17, 19]	15-25

7.2.3 Additional definitions

7.2.3.1 Elevated liver function

Elevated liver function tests were defined as the result being above the upper limit of normal (ULN) relative to the reported or imputed laboratory reference range. Elevated results were then categorised as being between 1 and 2x the ULN or above 2x the ULN.

7.2.4 Statistical analysis

Prevalence of elevated liver function tests were calculated as the number of people with an elevated result (or multiple elevated test results) divided by the number of participants with a valid test (or combination of tests). 95% CIs were calculated using the binomial distribution.

I examined the association between median age, sex and comorbidity and not having a valid liver function test result.

7.3 Results

7.3.1 Prevalence of elevated liver function

7.3.1.1 AST

I examined the proportion of patients who had an elevated AST test result based on the reference ranges given by their individual laboratory. Between 2.3% and 6.7% of the patients with a valid AST measurement had an elevated AST according to the reference ranges given (or imputed) by the laboratory (see Table 7-5). Using the median imputed reference ranges, 3.3% of participants had an elevated AST.

7.3.1.2 ALP

I examined the proportion of patients who had an elevated ALP test result based on the reference ranges given by their individual laboratory Between 5.8% and 41.3% of the patients with a valid ALP measurement had an elevated ALP according to the reference ranges given (or imputed) by the laboratory(see Table 7-6). Using the median imputed reference ranges, 9.2% of participants had an elevated ALP.

7.3.1.3 Bilirubin

I examined the proportion of patients who had an elevated bilirubin test result based on the reference ranges given by their individual laboratory. Between 3.6% and 7.2% of the patients with a valid bilirubin measurement had an elevated bilirubin according to the reference ranges given (or imputed) by the laboratory (see Table 7-7). Using the median imputed reference ranges, 5.4% of participants had an elevated bilirubin.

Table 7-5 Prevalence of elevated AST

	Above upper limit of reference n (% of those with valid test result)	Within reference range	Below lower limit of reference	No value for test	Total
Using median reference	429 (3.3)	12,287	110	2,482	15,308
Using minimum reference	865 (6.7)	11,851	110	2,482	15,308
Using maximum reference	301 (2.3)	12,415	110	2,482	15,308

Table 7-6 Prevalence of elevated ALP

	Above upper limit of reference n (% of those with valid test result)	Within reference range	Below lower limit of reference	No value for test	Total
Using median reference	1,246 (9.2)	12,207	46	1,809	15,308
Using minimum reference	5,572 (41.3)	7,881	46	1,809	15,308
Using maximum reference	783 (5.8)	12,670	46	1,809	15,308

Table 7-7 Prevalence of elevated bilirubin

	Above upper limit of reference n (% of those with valid test result)	Within reference range	Below lower limit of reference	No value for test	Total
Using median reference	690 (5.4)	11,980	20	2,618	15,308
Using minimum reference	918 (7.2)	11,752	20	2,618	15,308
Using maximum reference	452 (3.6)	12,218	20	2,618	15,308

7.3.1.4 Any elevated liver function

For the rest of the analyses imputation according to the median reference ranges is used.

Of 15 308 participants in the universal arm of the trial, 13 276 (86.7%) had at least one valid measurement of liver function. Participants who did not have a valid test result were more likely to be female (OR 1.33 [1.19, 1.49]), were slightly older (median age 81.5 years for those without a valid test result compared with 80.2 years for those with a test) and had more missing data with respect to comorbidity compared with those people who had at least one valid test result.

Overall, 16.1% of those with one or more valid measurement had at least one elevated liver function test. The most common elevated liver function test within this population was ALP with 9.2% (95%CI [8.7%, 9.7%]) of people having a result above the ULN (see Table 7-8). Only 5.4% (95%CI [5.0%, 5.8%]) of people had an elevated bilirubin test, whilst an even smaller proportion had an elevated AST result, 3.3% (95%CI [3.0%, 3.7%]) of those with a valid measurement. The majority of subjects with an elevated measurement had a test result less than or equal to 2x the ULN: 86.2% AST; 90.0% ALP, 93.8% bilirubin.

Table 7-8 Prevalence of elevated liver function tests

Elevated test(s) (Number with valid test)	Number elevated (% of elevated)	% of valid tests elevated [95% CI]
Any elevated (N=13546)	2175	16.1 [15.4, 16.7]
AST (N=12826)	429 (100)	3.34 [3.04, 3.67]
≤ 2x ULN	370 (86.2)	2.88 [2.60, 3.19]
Above 2x ULN	59 (13.8)	0.46 [0.35, 0.59]
ALP (N=13499)	1246 (100)	9.23 [8.75, 9.73]
≤ 2x ULN	1122 (90.0)	8.31 [7.85, 8.79]
Above 2x ULN	124 (10.0)	0.92 [0.76, 1.09]
Bilirubin (N=12690)	690 (100)	5.44 [5.05, 5.85]
≤ 2x ULN	647 (93.8)	5.10 [4.72, 5.50]
Above 2x ULN	43 (6.2)	0.34 [0.25, 0.46]
AST and ALP (N=12794)	90	0.70 [0.57, 0.86]
AST and bilirubin (N=12021)	42	0.35 [0.25, 0.47]
ALP and bilirubin (N=12648)	67	0.52 [0.41, 0.67]
AST, ALP and bilirubin (N=11994)	9	0.07 [0.03, 0.14]
All 3 within reference range (N=11994)	10025	83.6 [82.9, 84.2]

7.4 Discussion

7.4.1 Key findings

I found that nearly 1 in 6 of the general population aged 75 and over had at least one elevated liver function test. Over half of these abnormalities can be accounted for by an elevated measurement of ALP (9.2% of all subjects) and the vast majority were within 1x the upper limit of normal for the test measured. Very few participants had more than one recorded elevated liver function test (<1% for any combinations of one or more elevated liver function tests) with only 9 participants having all 3 liver function tests recorded as elevated.

7.4.2 Strengths and limitations

In this study I was able to assess, for the first time, the liver function of a representative randomly selected community-based sample of people aged 75 and over. That blood samples were available for most of the people in the MRC elderly gives this study a distinct advantage over many other studies looking at liver function insofar as the study population was not selected on the basis of known or suspected liver disease.

Arguably, abnormalities of AST, ALP and bilirubin are of secondary importance when looking at liver function compared with a measurement of alanine aminotransferase (ALT) which is specific to the liver. I was unable to investigate this as a blood test for this enzyme was not a part of the original study design.

As a result of the multi-site nature of this large study I was reliant on data collection from several laboratories across the UK. Not all laboratories were able to provide reference ranges for the liver function tests so I relied on imputation for nearly half of the reference ranges. Basing the upper limit of normal on the median reference range for those practices where imputation was necessary may under- or over-estimate the true level of elevated liver function in this population. This could make a significant difference to the proportion of older people who would be considered to have elevated liver function as seen particularly in the measurement of ALP. Using the minimum reference ranges for elevated upper limits an estimated 41.3% of participants had an elevated ALP test result compared with only 9.2% when using the median reference range.

Data having been collected from multiple laboratories also meant that I was unable to describe absolute values of enzymatic activity as there was not one uniform test in operation at all of the different sites.

In some laboratories there were different normal reference ranges provided for ALP for people aged 60 and above, those aged less than 60 and in some cases for children. It may be that reference ranges for the LFTs measured should be provided in even finer categories than this. I examine the association between abnormal measurements and age in the next chapter.

7.4.3 Comparison with previously published work

Information on the prevalence of elevated liver function in the UK is surprisingly lacking. These results show a lower prevalence of elevated transaminase (3.3% elevated AST vs. 7.0% elevated AST or alanine transaminase), ALP (9.2% vs. 10.4%) and bilirubin (5.4% vs. 7.1%) than those

reported in a recent study of adults of all ages from Scotland.[66] This is perhaps expected as the population within this study was selected on the basis that subjects already had a measurement of liver function contained within their primary care records. The authors acknowledge that they do not know why liver function tests were requested and this is likely to include the investigation of suspected liver disease leading to a non-representative sample of the general population.

In a study in America,[76] again only a selected group of participants had a blood test, and it is likely that the true population prevalence of elevated liver function tests may have been over estimated. Indeed, 12.8% of those with a measurement of AST had an elevated test, nearly four times that seen in my study. Another study from the USA also showed a slightly higher prevalence of elevated AST to that which I have described in this study, with 3.7% and 4.9% of the population aged 20 or over having an elevated AST in 1988-1994 and 1999-2002 respectively.[71] However, given that my study looks only at people aged 75 and over, it may be that the prevalence of elevated liver function tests in a population of older people is indeed lower than that found in the general adult population of all ages. This is supported by data from America where the prevalence of elevated ALT or AST in the population aged 70 or older was reported as 4.9%, statistically significantly lower than the prevalence of elevated transaminases in younger age groups.[70]

7.4.4 Conclusions

Current guidelines recommend that liver function tests should be carried out before and within 1-3 months of starting treatment on statins to monitor for signs of altered liver function.[111] With an estimated 40% of all 75-79 year olds have at least one prescription for statins annually,[112] incidental findings of

elevated LFTs in this age group of the population in the absence of symptoms are likely to occur regularly. The study reported in this chapter has shown that abnormalities in liver function are fairly common in people aged 75 and over. Using population estimates for 2008 if every person aged 75 and over was to undergo these three blood tests elevated levels in one or more of the LFTs would be found in 770,000 patients. It will be important to determine the correct course of action for the follow-up and assessment of older people with elevated liver function tests to avoid unnecessary follow-up and investigation and potential anxiety for an individual.

8 Demographic, lifestyle and medical characteristics associated with an elevated liver function test

8.1 Introduction

This study aims to examine the association between elevated liver function tests and selected demographic, lifestyle and clinical characteristics in people aged 75 and over.

8.2 Methods

8.2.1 Dataset used

The data used in this study are those from the detailed nurse assessment contained within the 'detail' database (see Figure 6-2). A total of 15,308 participants aged 75 and over are included in the subsequent analyses. The definition of elevated liver function is as described in section 7.2.3.1 following imputation of missing upper limits using the median reference ranges.

8.2.2 Additional definitions

8.2.2.1 Alcohol consumption

Alcohol consumption was calculated as the total number of self-reported units of alcohol consumed as beer (assuming one unit per half pint), wine (assuming one unit per glass of wine, sherry or port) and spirits (assuming one unit in a single measure) in the past week. Intake was then categorised as none and in seven-unit increments.

8.2.2.2 Smoking

Smoking status was recorded at the time of interview as either current smoker, ex-smoker or never a smoker.

8.2.2.3 Body Mass Index

Body Mass Index (BMI) was defined as weight (in kg) divided by height (in m) squared, each of which were measured once only. I subsequently categorised BMI into clinically recognised categories: <18.5 (underweight), 18.5-24.9 (normal weight), 25.0-29.9 (overweight) and 30+ (obese).

8.2.2.4 Waist:hip ratio

Waist circumference was measured to the nearest 0.1cm midway between the iliac crest and the lower rib margin by using an insertion tape. Hip circumference was measured as the widest circumference over the buttocks and below the iliac crest. Hip and waist were both measured twice (having asked patients to roll down their undergarments) and an average of the two values used in the calculation of waist:hip ratio (WHR).

8.2.2.5 Comorbidities

Diabetes was classified as present following either a self-reported medical diagnosis, prescription of anti-diabetic medication or a single high random blood glucose measurement.[113] Heart attack, hypertension, stroke, cancer and ulcer were defined as a positive self-reported medical diagnosis. Angina was defined as full angina as per the Rose score.[114] Dementia was defined as a score of <9 on the mini-mental state examination.[115]

In order to assess the potential for correlation between multiple co-morbid illnesses I derived a co-morbidity score. A patient was given a score of zero (not present) or one (present ever before the date of interview) for each of the following self-reported medical conditions:, asthma, stomach / digestive ulcer,

hypertension, heart attack, stroke, fractured hip or spine (within last year only), Parkinson's disease, cancer, and for each of the following: angina, dementia and diabetes (as per definitions above). Scores were added together to give an overall score and then categorised into 0, 1, 2 and 3 or more comorbidities.

8.2.3 Statistical analysis

To examine the association between elevated liver function tests and demographic, lifestyle and medical characteristics I used logistic regression to calculate odds ratios and 95% CIs. Analysis was performed treating an individual practice as a clustered unit with a random effects model employed. After univariable analyses, a priori confounders of age, sex and comorbidity plus additional statistically significant associations were built into a multivariable logistic regression model to account for potential confounding. Multivariable models were constructed in 2 ways. Firstly, missing values for covariables were modelled as a separate category to ensure all subjects remained within the analysis. Secondly, multivariable models were fitted using only participants with complete data and modelling continuous variables as linear trends.

8.3 Results

8.3.1 AST

Of the 12,836 participants with a valid measurement of AST, 429 (3.3%) had an elevated serum level of AST (as reported in section 7.3.1.1).

8.3.1.1 Univariable associations

Sex

Of those with an elevated AST 60% were female which was not statistically different to the 61% of those with a normal measurement of AST, OR 0.96 (95%CI [0.79, 1.18]) (see Table 8-1).

Age

Participants with an elevated AST were more likely to be younger than those with a normal AST measurement. For example, those over 90 years of age were 50% less likely to have an abnormal AST measurement than those aged 75. The odds ratio for a yearly increase in age fitted a linear trend and was 0.97 (95% CI[0.94, 0.99]).

Alcohol consumption

Data on total number of units of alcohol consumed in the previous week were missing for 18.5% of those with a normal AST and for 16.1% of those with an elevated AST. A further 35.9% of both groups recorded no consumption of alcohol within the previous week. There was a statistically significant association between alcohol consumption and an elevated AST with an odds ratio of 1.22 (95% CI[1.08, 1.37]) for each 7-unit increase in weekly consumption. Patients reported as consuming 22 or more units of alcohol in a

week were over twice as likely to have an elevated AST measurement than those who did not drink any alcohol.

Smoking

A much smaller percentage of participants had missing data on smoking compared with alcohol consumption, only 2.7% compared with 18.4% respectively. There was no statistically significant association between elevated AST and either being an ex- or current smoker compared with being classified as a never smoker.

Body size (BMI and WHR)

The majority of participants (52.8%) were recorded as being overweight or obese i.e. having a BMI of 25 or above with a further 8.5% having missing data on BMI. Having an elevated AST was not associated with either a low or high BMI. Having a higher waist-to-hip ratio was associated with elevated AST. For example, the odds of having an elevated AST if you had a WHR of between 1.05 and 1.15 were over 3 times that compared to if you had a WHR of between 0.75 and 0.84. Although no other individual category of WHR conferred a statistically significant association with elevated AST when examined a continuous categorical variable there was an association with higher WHR group and elevated AST (OR 1.17 (95% CI[1.03, 1.32])).

Comorbidities

Of the comorbidities examined only diabetes and dementia were seen to be associated with an elevated AST. Having had a heart attack, hypertension, a stroke, cancer, ulcer or angina were not statistically significantly associated with an elevated AST. When examining comorbidity as a composite score

there was no statistically significant association seen between the derived comorbidity index and elevation of AST.

8.3.1.2 Multivariable associations

To build the multivariable model a priori confounders of age, sex and comorbidity as well as alcohol consumption and WHR were included. Upon adjustment there remained a statistically significant association between elevated AST and age, alcohol consumption and high WHR (see Table 8-1). There was no evidence of substantial confounding with the exception of the estimates for the association with sex which increased following adjustment for age, alcohol consumption, WHR and comorbidity. The change in association between sex and elevated AST suggested some form of interaction. Fitting a third multivariable model including an interaction term for age and sex led to a further slight increase in the association between being female and having an elevated measurement of AST.

Table 8-1 Associations between elevated AST test and demographic, lifestyle and clinical characteristics

	Normal AST (N=12397)		Elevated AST (N=429)		OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
	N	%	N	%	Univariable	Model 1*	Model 2*	Model 3*
Sex								
Male	4838	39.0	173	40.0	-	-		
Female	7559	61.0	256	60.0	0.96 [0.79, 1.18]	1.27 [0.98, 1.64]	1.34 [1.01, 1.78]	1.47 [0.99, 2.18]
Age (years)								
Median age [IQR] (range)	80.2 [77.2, 84.2] (75, 108)		79.2 [77, 83.2] (75, 99)					
75-	1099	8.9	56	13.1	-	-		
76-	1569	12.7	52	12.1	0.70 [0.47, 1.05]	0.70 [0.47, 1.04]		
77-	1300	10.5	55	12.8	0.90 [0.60, 1.33]	0.89 [0.60, 1.33]		
78-	936	7.6	41	9.6	0.95 [0.62, 1.45]	0.94 [0.61, 1.45]		
79-	943	7.6	29	6.8	0.66 [0.41, 1.06]	0.67 [0.41, 1.07]		
80-	878	7.1	25	5.8	0.59 [0.36, 0.96]	0.59 [0.36, 0.97]		
81-	874	7.1	35	8.2	0.85 [0.54, 1.32]	0.87 [0.55, 1.36]		
82-	774	6.2	25	5.8	0.67 [0.41, 1.11]	0.70 [0.43, 1.16]		
83-	706	5.7	17	4.0	0.46 [0.26, 0.80]	0.47 [0.27, 0.84]		
84-	624	5.0	18	4.2	0.63 [0.36, 1.10]	0.65 [0.37, 1.13]		
85-	527	4.3	15	3.5	0.61 [0.34, 1.10]	0.62 [0.34, 1.13]		
86-	449	3.6	13	3.0	0.65 [0.35, 1.22]	0.68 [0.36, 1.28]		
87-	404	3.3	10	2.3	0.52 [0.26, 1.04]	0.54 [0.27, 1.09]		
88-	323	2.6	13	3.0	0.89 [0.47, 1.69]	0.93 [0.49, 1.76]		
89-	264	2.1	9	2.1	0.69 [0.33, 1.43]	0.71 [0.34, 1.49]		
90+	665	5.4	16	3.7	0.49 [0.28, 0.88]	0.52 [0.29, 0.94]		
Missing	62	0.5	0	0	-	-		

Odds ratio for yearly increase in age					0.97 [0.94, 0.99]		0.97 [0.94, 1.00]	1.00 [0.91, 1.10]
Alcohol								
Median units of alcohol intake in past week [IQR] (range)	1 [0,4] (0,90) N=10106		1 [0,7] (0,87) N=360					
Alcohol units								
0	4453	35.9	154	35.9	-			
1-	4341	35.0	133	31.0	0.86 [0.68, 1.10]	0.86 [0.67, 1.10]		
8-	856	6.9	43	10.0	1.54 [1.07, 2.21]	1.51 [1.04, 2.20]		
15-	250	2.0	15	3.5	1.85 [1.04, 3.29]	1.83 [1.02, 3.28]		
22+	206	1.7	15	3.5	2.36 [1.33, 4.22]	2.37 [1.31, 4.30]		
Missing	2291	18.5	69	16.1	0.85 [0.63, 1.15]	0.86 [0.64, 1.17]		
Odds ratio for step increase in alcohol					1.22 [1.08, 1.37]		1.16 [1.02, 1.32]	1.16 [1.02, 1.32]
Smoking								
Never	4774	38.5	177	41.3				
Ex	6081	49.1	200	46.6	0.86 [0.70, 1.07]			
Current	1200	9.7	47	11.0	0.97 [0.69, 1.35]			
Missing	342	2.8	5	1.2	0.48 [0.19, 1.19]			
BMI group								
<18.5	253	2.0	6	1.4	0.73 [0.32, 1.69]			
18.5-	4541	36.6	152	35.4	-			
25-	4719	38.1	167	38.9	1.08 [0.86, 1.36]			
30-	1495	12.1	61	14.2	1.26 [0.92, 1.72]			
35+	328	2.7	14	3.3	1.28 [0.72, 2.27]			
Missing	1061	8.6	29	6.8	0.95 [0.62, 1.43]			
Increase in BMI group					1.11 [0.98, 1.26]			

Waist:hip								
0.65-0.74	421	3.4	10	2.3	0.81 [0.42, 1.56]	0.80 [0.41, 1.56]		
0.75-0.84	3908	31.5	127	29.6				
0.85-0.94	4775	38.5	175	40.8	1.10 [0.86, 1.39]	1.13 [0.87, 1.47]		
0.95-1.04	2161	17.4	74	17.3	1.12 [0.83, 1.51]	1.14 [0.80, 1.63]		
1.05-1.15	197	1.6	17	4.0	3.26 [1.88, 5.65]	3.22 [1.79, 5.80]		
Missing	935	7.5	26	6.1	1.00 [0.65, 1.56]	1.10 [0.70, 1.73]		
Increase in waist:hip ratio group					1.17 [1.03, 1.32]		1.27 [1.07, 1.50]	1.27 [1.08, 1.50]
Presence of Co-morbidity								
Diabetes	977	7.9	48	11.2	1.53 [1.12, 2.10]			
Heart attack	1319	10.6	39	9.1	0.87 [0.62, 1.22]			
Hypertension	4121	33.2	152	35.4	1.13 [0.92, 1.39]			
Stroke	1070	8.6	36	8.4	1.04 [0.73, 1.49]			
Cancer	1272	10.3	45	10.5	1.09 [0.79, 1.50]			
Ulcer	1476	11.9	57	13.3	1.15 [0.86, 1.54]			
Angina	778	6.3	23	5.4	0.88 [0.57, 1.36]			
Dementia	80	0.7	6	1.4	2.71 [1.15, 6.37]			
Co-morbidity score								
0	4427	34.5	852	34.3				
1	4809	37.5	850	34.3	1.14 [0.90, 1.44]	1.11 [0.88, 1.41]		
2	2353	18.4	442	17.8	1.21 [0.91, 1.61]	1.18 [0.88, 1.57]		
3+	1036	8.1	189	7.6	1.27 [0.87, 1.84]	1.23 [0.84, 1.80]		
Missing	201	1.6	149	6.0	0.80 [0.34, 1.87]	0.81 [0.34, 1.94]		
Odds ratio for increase in co-morbidity score					1.09 [0.98, 1.21]		1.08 [0.96, 1.22]	1.08 [0.96, 1.22]

*Multivariable model 1 adjusted for sex, age, alcohol consumption, WHR and comorbidity as categorical variables; model 2 using only subjects with complete data adjusted for sex plus age, alcohol consumption, WHR and comorbidity fitted as linear trend variables; model 3 as model 2 with an interaction term for age and sex.

8.3.2 ALP

Of the 13,499 participants with a valid measurement of ALP, 1246 (9.2%) had an elevated serum level of ALP (as reported in section 7.3.1.2).

8.3.2.1 Univariable associations

Sex

Of those with an elevated ALP 62.9% were female which was not statistically different to the 60.9% of those with a normal measurement of ALP, OR 1.05 (95%CI [0.93, 1.19]) (see Table 8-2).

Age

In direct contrast to that seen with elevations of AST (section 8.3.1 above) participants with an elevated ALP were more likely to be older than those with a normal ALP measurement, the odds ratio for a yearly increase in age being 1.05 (95% CI[1.04, 1.07]). Those aged 90 and over were twice as likely to have an elevated measurement of ALP than those aged 75.

Alcohol consumption

There was a statistically significant association between lower alcohol consumption and an elevated ALP with an odds ratio of 0.81 (95% CI[0.74, 0.88]) for each 7-unit increase in weekly consumption meaning that for each additional 7 units consumed in a week participants were 20% less likely to have a measurement of elevated ALP. Those participants reported as consuming 22 or more units of alcohol per week were 50% less likely to have an elevated measurement of ALP than those who did not report consuming any alcohol.

Smoking

There was no statistically significant association between elevated ALP and being a current smoker but there was a small 'protective' effect conferred in those recorded as ex-smokers with an odds ratio of 0.82 (95% CI[0.72, 0.94]) of having an elevated ALP compared with never smokers.

Body size (BMI and WHR)

There was no trend in association seen with increasing BMI category and elevated ALP. However, those participants in the highest BMI category – severely obese (BMI 35 or more) – had a 50% greater chance of having an elevated ALP (OR 1.52 (95% CI[1.10, 2.10])). There were no statistically significant associations seen between WHR and elevated ALP measurement.

Comorbidities

Reported history of diabetes and heart attack were associated with an elevated ALP (OR 1.64 (95% CI[1.35, 1.99]) and 1.24 (95% CI[1.03, 1.49]) respectively). Additionally an assessment of dementia was significantly associated with an elevated measurement of ALP (OR 2.64 (95% CI[1.58, 4.42])).

8.3.2.2 Multivariable associations

To build the multivariable model a priori confounders of age, sex and comorbidity as well as alcohol consumption were included. Upon adjustment there remained a statistically significant association between elevated ALP and age, alcohol consumption and comorbidity score (see Table 8-2).

Table 8-2 Associations between demographic, lifestyle and medical characteristics and elevated ALP test

	Normal ALP (N=12253)		Elevated ALP (N=1246)		OR [95% CI]	OR [95% CI]	
	N	%	N	%	Univariable	Model 1*	Model 2*
Sex							
Female	7456	60.9	784	62.9	1.05 [0.93, 1.19]	0.90 [0.79, 1.03]	0.94 [0.80, 1.09]
Male	4797	39.1	462	37.1			
Age (years)							
Median age [IQR]	80.2 [77.2, 84.0]		81.4 [77.6, 85.8]				
(range)	(75, 108)		(75, 98)				
75-	1127	9.2	87	7.0	-	-	-
76-	1581	12.9	139	11.2	1.01 [0.76, 1.34]	1.02 [0.76, 1.35]	
77-	1319	10.8	106	8.5	0.95 [0.71, 1.29]	0.96 [0.71, 1.30]	
78-	939	7.7	81	6.5	1.01 [0.73, 1.40]	1.01 [0.73, 1.39]	
79-	927	7.6	89	7.1	1.14 [0.83, 1.56]	1.12 [0.82, 1.54]	
80-	893	7.3	67	5.4	0.85 [0.61, 1.19]	0.83 [0.59, 1.16]	
81-	861	7.0	77	6.2	1.07 [0.77, 1.49]	1.06 [0.76, 1.47]	
82-	767	6.3	83	6.7	1.28 [0.93, 1.77]	1.24 [0.90, 1.72]	
83-	689	5.6	77	6.2	1.29 [0.92, 1.79]	1.25 [0.90, 1.74]	
84-	609	5.0	71	5.7	1.42 [1.01, 1.99]	1.37 [0.97, 1.92]	
85-	515	4.2	61	4.9	1.35 [0.95, 1.92]	1.30 [0.91, 1.85]	
86-	428	3.5	51	4.1	1.40 [0.96, 2.04]	1.34 [0.92, 1.95]	
87-	385	3.1	49	3.9	1.56 [1.07, 2.28]	1.47 [1.00, 2.15]	
88-	319	2.6	34	2.7	1.22 [0.80, 1.88]	1.16 [0.76, 1.79]	
89-	240	2.0	46	3.7	2.39 [1.60, 3.56]	2.29 [1.53, 3.42]	
90+	600	4.9	117	9.4	2.40 [1.77, 3.25]	2.33 [1.71, 3.17]	
Missing	54	0.4	11	0.9	2.54 [1.24, 5.21]	2.38 [1.16, 4.90]	

Odds ratio for yearly increase in age					1.05 [1.04, 1.07]		1.05 [1.03, 1.06]
Alcohol							
Median units of alcohol intake in past week	1 [0,4] (0,90) N=10008		1 [0,4] (0,87) N=960				
Alcohol units							
0	4369	35.7	493	39.6	-		
1-	4305	35.1	356	28.6	0.70 [0.61, 0.82]	0.72 [0.62, 0.83]	
8-	866	7.1	77	6.2	0.71 [0.55, 0.92]	0.71 [0.54, 0.93]	
15-	251	2.1	20	1.6	0.54 [0.34, 0.88]	0.57 [0.35, 0.93]	
22+	217	1.8	14	1.1	0.49 [0.28, 0.86]	0.49 [0.28, 0.87]	
Missing	2245	18.3	286	23.0	1.09 [0.93, 1.29]	1.04 [0.89, 1.23]	
Odds ratio for increase in alcohol group					0.81 [0.74, 0.88]		0.83 [0.76, 0.91]
Smoking							
Never	4696	38.3	519	41.7			
Ex	6028	49.2	557	44.7	0.82 [0.72, 0.94]	0.92 [0.80, 1.06]	0.91 [0.77, 1.06]
Current	1189	9.7	142	11.4	1.06 [0.86, 1.29]	1.22 [0.99, 1.51]	1.25 [0.98, 1.58]
Missing	340	2.8	28	2.3	0.79 [0.52, 1.18]	0.76 [0.50, 1.15]	
BMI group							
<18.5	239	2.0	34	2.7	1.36 [0.93, 1.99]		
18.5-	4470	36.5	475	38.1	-		
25-	4709	38.4	414	33.2	0.85 [0.74, 0.98]		
30-	1521	12.4	125	10.0	0.79 [0.64, 0.98]		
35+	317	2.6	51	4.1	1.52 [1.10, 2.10]		
Missing	997	8.1	147	11.8	1.57 [1.28, 1.94]		
				Trend	0.95 [0.88, 1.03]		

Waist:hip							
0.65-0.74	411	3.4	40	3.2	1.02 [0.72, 1.45]		
0.75-0.84	3886	31.7	367	29.5	-		
0.85-0.94	4721	38.5	499	40.1	1.09 [0.94, 1.26]		
0.95-1.04	2130	17.4	196	15.7	0.99 [0.83, 1.21]		
1.05-1.15	204	1.7	16	1.3	0.90 [0.53, 1.54]		
Missing	901	7.4	128	10.3	1.75 [1.40, 2.19]		
				Trend	1.00 [0.93, 1.08]		
Presence of Co-morbidity							
Diabetes	925	7.6	144	11.6	1.64 [1.35, 1.99]		
Heart attack	1277	10.4	159	12.8	1.24 [1.03, 1.49]		
Hypertension	4114	33.6	388	31.1	0.89 [0.78, 1.01]		
Stroke	1045	8.5	111	8.9	1.05 [0.85, 1.29]		
Cancer	1242	10.1	126	10.1	0.97 [0.80, 1.19]		
Ulcer	1461	11.9	159	12.8	1.11 [0.92, 1.32]		
Angina	753	6.2	82	6.6	1.02 [0.80, 1.30]		
Dementia	77	0.6	20	1.6	2.64 [1.58, 4.42]		
Co-morbidity score							
0	4262	34.8	413	33.2	-	-	
1	4593	37.5	468	37.6	1.06 [0.92, 1.22]	1.08 [0.94, 1.25]	
2	2238	18.3	228	18.3	1.04 [0.87, 1.24]	1.08 [0.91, 1.29]	
3+	972	7.9	115	9.2	1.25 [1.00, 1.57]	1.29 [1.03, 1.62]	
Missing	188	1.5	22	1.8	1.45 [0.91, 2.31]	1.22 [0.76, 1.96]	
Odds ratio for increase in co-morbidity score					1.05 [0.99, 1.12]		1.12 [1.04, 1.21]

*Multivariable model 1 adjusted for sex, age, alcohol consumption, smoking status and comorbidity as categorical variables; model 2 using only subjects with complete data adjusted for sex, smoking status plus age, alcohol consumption and comorbidity fitted as linear trend variables

8.3.3 Bilirubin

Of the 12,690 participants with a valid measurement of bilirubin, 690 (5.4 %) had an elevated serum level of bilirubin (as reported in section 7.3.1.3).

8.3.3.1 Univariable associations

Sex

Of those with an elevated bilirubin only 38.3% were female which was significantly different to the 62.4% of those with a normal measurement of bilirubin (OR 0.37 (95%CI [0.32, 0.44])) (see Table 8-3).

Age

Unlike with AST and ALP there was no association seen between elevated bilirubin and age (OR 0.99 (95% CI[0.97, 1.01])).

Alcohol consumption

There was a statistically significant association between higher alcohol consumption and an elevated bilirubin with an odds ratio of 1.20 (95% CI[1.09, 1.31]) for each 7-unit increase in weekly consumption meaning that for each additional 7 units consumed in a week a participants were 20% more likely to have a measurement of elevated bilirubin. Those participants who reported consuming 22 or more units of alcohol in a week were over twice as likely to have an measurement of elevated bilirubin compared to those who did not consume any alcohol.

Smoking

There was a statistically significant association between elevated bilirubin and being an ex-smoker (OR 1.22 (95% CI[1.03, 1.44])) but there was no association for those recorded as current smokers compared with never smokers (OR 0.76 (95% CI[0.56, 1.05])).

Body Size (BMI and WHR)

There was no trend in association seen with increasing BMI category and elevated bilirubin. However, those participants in the highest BMI category – severely obese (BMI 35 or more) – had a greater than 50% reduction in the chance of having an elevated bilirubin measurement (OR 0.44 (95% CI[0.22, 0.86])). There was a statistically significant association seen in increasing WHR and elevated bilirubin with each increase in WHR category conferring a 27% increase in odds of having an elevated bilirubin (OR 1.27 (95% CI[1.15, 1.40])).

Comorbidities

None of the individual comorbidities examined showed any association with elevated bilirubin. Unsurprisingly, when examining comorbidity as a composite score there was no statistically significant association seen between increasing score in the derived comorbidity index and elevation of bilirubin.

8.3.3.2 Multivariable associations

To build the multivariable model a priori confounders of age, sex and comorbidity as well as alcohol consumption, smoking and WHR were included. Upon adjustment there remained a statistically significant

association between elevated bilirubin and sex but the associations between alcohol consumption and WHR with elevated bilirubin were removed (see Table 8-3)

Table 8-3 Associations between demographic, lifestyle and medical characteristics and an elevated bilirubin test

	Normal bilirubin (N=12000)		Elevated bilirubin (N=690)		OR [95% CI]	Adjusted OR [95% CI]	Adjusted OR [95% CI]
	N	%	N	%	Univariable	Model 1*	Model 2*
Sex							
Male	4518	37.6	426	61.7	-		
Female	7482	62.4	264	38.3	0.37 [0.32, 0.44]	0.33 [0.27, 0.41]	0.33 [0.26, 0.42]
Age (years)							
Median age [IQR] (range)	80.2 [77.2, 84.1] (75, 108)		80.0 [77.0, 83.4] (75, 98)				
75-	1056	8.8	66	9.6	-	-	
76-	1536	12.8	98	14.2	0.99 [0.71, 1.37]	0.99 [0.71, 1.37]	
77-	1261	10.5	66	9.6	0.83 [0.58, 1.18]	0.83 [0.58, 1.19]	
78-	934	7.8	50	7.3	0.82 [0.56, 1.20]	0.83 [0.57, 1.23]	
79-	899	7.5	59	8.6	1.03 [0.71, 1.48]	1.04 [0.72, 1.51]	
80-	865	7.2	42	6.1	0.75 [0.50, 1.12]	0.79 [0.52, 1.18]	
81-	831	6.9	55	8.0	1.00 [0.69, 1.46]	1.05 [0.71, 1.53]	
82-	748	6.2	53	7.7	1.11 [0.76, 1.62]	1.21 [0.83, 1.78]	
83-	681	5.7	40	5.8	0.94 [0.62, 1.41]	0.99 [0.65, 1.50]	
84-	604	5.0	27	3.9	0.69 [0.43, 1.10]	0.72 [0.45, 1.16]	
85-	515	4.3	26	3.8	0.79 [0.49, 1.26]	0.80 [0.50, 1.30]	
86-	436	3.6	15	2.2	0.53 [0.30, 0.94]	0.56 [0.31, 1.01]	
87-	380	3.2	30	4.4	1.22 [0.77, 1.92]	1.36 [0.86, 2.16]	
88-	318	2.7	15	2.2	0.75 [0.42, 1.34]	0.86 [0.48, 1.55]	
89-	257	2.1	12	1.7	0.70 [0.37, 1.33]	0.79 [0.41, 1.50]	
90+	623	5.2	29	4.2	0.73 [0.46, 1.15]	0.87 [0.55, 1.39]	
Missing	56	0.5	7	1.0	1.71 [0.74, 3.98]	1.75 [0.74, 4.14]	

Odds ratio for yearly increase in age					0.99 [0.97, 1.01]		0.99 [0.97, 1.01]
Alcohol							
Median units of alcohol intake in past week	1 [0, 4] (0, 90) N=9746		1 [0, 6] (0, 44) N=585				
Alcohol units							
0	4361	36.3	234	33.9	-		
1-	4117	34.3	251	36.4	1.15 [0.96, 1.39]	1.02 [0.85, 1.24]	
8-	830	6.9	61	8.8	1.42 [1.05, 1.91]	1.04 [0.76, 1.41]	
15-	243	2.0	19	2.8	1.60 [0.98, 2.63]	1.10 [0.66, 1.81]	
22+	195	1.6	20	2.9	2.24 [1.37, 3.66]	1.45 [0.88, 2.40]	
Missing	2254	18.8	105	15.2	0.90 [0.71, 1.15]	0.94 [0.73, 1.20]	
Odds ratio for increase in alcohol group					1.20 [1.09, 1.31]		1.06 [0.96, 1.18]
Smoking							
Never	4617	38.5	244	35.4			
Ex	5823	48.5	381	55.2	1.22 [1.03, 1.44]	0.83 [0.69, 1.00]	0.79 [0.65, 0.97]
Current	1212	10.1	50	7.3	0.76 [0.56, 1.05]	0.53 [0.38, 0.73]	0.47 [0.32, 0.68]
Missing	348	2.9	15	2.2	0.86 [0.50, 1.48]	0.63 [0.36, 1.10]	
BMI group							
<18.5	247	2.1	14	2.0	0.95 [0.54, 1.66]		
18.5-	4402	36.7	256	37.1	-		
25-	4504	37.5	292	42.3	1.10 [0.92, 1.31]		
30-	1452	12.1	79	11.5	0.91 [0.70, 1.19]		
35+	333	2.8	9	1.3	0.44 [0.22, 0.86]		
Missing	1062	8.9	40	5.8	0.67 [0.47, 0.94]		
Odds ratio for increase in BMI group					0.94 [0.85, 1.04]		

Waist:hip							
0.65-0.74	391	3.3	20	2.9	1.36 [0.84, 2.20]	1.51 [0.93, 2.45]	
0.75-0.84	3827	31.9	149	21.6			
0.85-0.94	4608	38.4	314	45.5	1.73 [1.41, 2.12]	1.07 [0.85, 1.34]	
0.95-1.04	2008	16.7	154	22.3	1.88 [1.48, 2.38]	0.86 [0.65, 1.13]	
1.05-1.15	195	1.6	15	2.2	1.65 [0.94, 2.90]	0.75 [0.41, 1.35]	
Missing	971	8.1	38	5.5	1.00 [0.69, 1.45]	0.72 [0.49, 1.06]	
				Trend	1.27 [1.15, 1.40]		0.90 [0.79, 1.03]
Presence of Co-morbidity							
Diabetes	941	7.8	61	8.8	1.12 [0.85, 1.48]		
Heart attack	1283	10.7	71	10.3	0.97 [0.75, 1.25]		
Hypertension	3987	33.2	231	33.5	1.00 [0.85, 1.18]		
Stroke	1041	8.7	48	7.0	0.77 [0.57, 1.04]		
Cancer	1219	10.2	62	9.0	0.90 [0.68, 1.17]		
Ulcer	1446	12.1	91	13.2	1.14 [0.90, 1.43]		
Angina	746	6.2	47	6.8	1.14 [0.84, 1.56]		
Dementia	92	0.8	2	0.3	0.38 [0.09, 1.54]		
Co-morbidity score							
0	4152	34.6	238	34.5	-		
1	4502	37.5	254	36.8	0.99 [0.82, 1.19]	0.98 [0.81, 1.18]	
2	2174	18.1	137	19.9	1.10 [0.88, 1.37]	1.07 [0.85, 1.34]	
3+	980	8.2	48	7.0	0.87 [0.63, 1.21]	0.86 [0.65, 1.13]	
Missing	192	1.6	13	1.9	1.30 [0.72, 2.34]	0.75 [0.41, 1.35]	
Odds ratio for increase in co-morbidity score					0.99 [0.91, 1.07]		0.98 [0.89, 1.08]

*Multivariable model 1 adjusted for sex, age, alcohol consumption, smoking status, WHR and comorbidity as categorical variables; model 2 using only subjects with complete data adjusted for sex, smoking status plus age, alcohol consumption, WHR and comorbidity fitted as linear trend variables

8.4 Discussion

8.4.1 Key findings

This study has determined the associations between elevated LFTs and various demographic, lifestyle and clinical characteristics in a population of people aged 75 and over.

Of note were the observed associations between age and alcohol consumption with elevated AST and ALP. The odds ratios for the associations between AST and these variables were almost exactly the inverse of the associations seen between ALP and these variables. Increasing age was associated with a decreased risk of an elevated measurement of AST (adjusted OR for 1-year increase in age 0.97 (95% CI[0.94, 0.99])) but an increased risk of an elevated measurement of ALP (adjusted OR for 1-year increase in age 1.04 (95% CI[1.03, 1.06])). Increasing alcohol consumption was associated with an increased risk of an elevated measurement of AST (adjusted OR for seven unit increase in alcohol consumption 1.16 (95% CI[1.02, 1.32])) but a decreased risk of an elevated measurement of ALP (adjusted OR for seven unit increase in alcohol consumption 0.83 (95% CI[0.76, 0.91])).

Both elevated AST and ALP were shown to be associated with the diagnosis of diabetes and dementia. Additionally elevated ALP was associated with heart attack.

Being male was very highly associated with having a abnormal measurement of bilirubin (adjusted OR for elevated bilirubin for females 0.45 (95% CI[0.35, 0.58])). Upon multivariable adjustment both being an ex-smoker or a current smoker appeared to confer some protection against having an elevated bilirubin measurement.

8.4.2 Strengths and limitations

This study relied on a single measurement of each of AST, ALP and bilirubin. Naturally it would be desirable to have multiple measurements of these liver function tests in order to assess whether an abnormality was persistent and therefore that there was a consistent association with any given characteristic of interest.

Although I have been able to examine the associations of several characteristics with elevated LFTs in this large population there are limitations in the interpretation of these findings resulting from the absence of particular data items from the initial data collection. Particularly the absence of data on diagnosed or recognised liver disease means that I am not able to exclude the presence of liver disease as a potential confounder of any of the associations seen. The examination of so many associations will also potentially have led to some statistically significant findings occurring just through chance alone.

I was able to examine the associations between several individual diseases and elevated LFTs as well as a derived comorbidity index. The derivation of a comorbidity index was a pragmatic approach to try and account for the potential for multiple diseases to be present in one individual. As I was analysing these data as a secondary source it was not possible to derive a more recognised comorbidity index, such as the Charlson score (described in section 4.2.2) as several of the data items needed to create such a score were not available from the original questionnaires.

As well as not being able to adjust for some relevant comorbidity it was also not possible to adjust for any medications that the participants may have been

taking (as this information was not available to me) which may have affected the levels of serum enzymes recorded. However, the adjusted odds ratios include a measure of comorbidity which may have partially taken this into account.

As with any cross-sectional study it is not possible to infer anything regarding causality from these results. For example, it is equally possible that having had a heart attack led to an elevation in ALP or that the underlying reason for the elevation in ALP was also the mechanism that led to the heart attack. Either pathway would result in a positive association as seen in these data.

8.4.3 Comparison with previous studies

As discussed in section 1.4.2.2 there have been a number of studies reporting associations between various characteristics and elevated LFTs but with little consistency in the definition of abnormality and some disagreement in the direction and magnitude of the associations. Many of these studies have also focussed on abnormalities in transaminases, considering elevations of AST and ALT together, with a lack of data on individual elevations of AST, ALP or bilirubin.

The recent study of residents in Tayside, Scotland with a measurement of liver function showed a very different pattern of association with comorbidity to that which I have described in this study.[66] An elevated measurement of ALP was associated with a statistically significant lower risk of several comorbidities (ischaemic heart disease, diabetes, respiratory disease and cancer) but with a slightly higher risk of biliary disease probably reflecting the selection bias inherent in this study. My analysis has shown an increased risk of diabetes,

heart attack and dementia with elevated ALP. In the study in Tayside, an elevated measurement of bilirubin was associated with a statistically significant lower risk of all of these comorbidities with the exception of diabetes in contrast with my analysis where there was no association between bilirubin and any of the diagnosed or self-reported diseases recorded. However, the proportion of patients within this study with these diagnosed co-morbidities is much lower than that seen in my study, perhaps reflecting the older age group of my study.

Similar to the results shown in section 8.3.1 the authors of the study in Scotland showed a higher proportion of patients with elevated transaminases to have a record of alcohol abuse.[66] However, they did not present any data on actual alcohol consumption. In contrast to my results in section 8.3.2 they also report a higher proportion of patients with an elevated ALP to have a record of alcohol abuse.

One study from America showed a lower prevalence of elevated aminotransferases in older ages (70+), which would be consistent with my findings of lower risk of elevated AST with increasing age, but there were no details presented at the fine level as in my study.[70]

Several studies report an association between an elevated measurement of AST and the presence or development of diabetes similar to that seen in my study. [68 70 73 74]

Many studies also report an association between increasing BMI and elevated liver function tests, particularly transaminases.[69 70 71 75] I did not see a relationship between increasing BMI and elevated liver function but did observe a relationship between increasing WHR category and elevated AST and also elevated bilirubin. This is possibly due to the fact that WHR is

considered a more accurate assessment of body fatness in older people owing to the increase in BMI that will occur as a result of shortening height.[116] A similar relationship as I have described between increasing alcohol consumption and elevated transaminases has previously been shown in studies in both the USA and South Korea.[68 71 75] Another study has not shown this relationship though it is hard to directly compare my data with this study as they classify drinkers as simply more or less than 3 units per day as opposed to examining a trend in increasing consumption.[69]

8.4.4 Conclusions

This study has shown a number of potentially interesting associations between demographic, lifestyle and clinical factors and elevated liver function tests. That the results for measurement of elevated AST and ALP with respect to age and alcohol are almost the exact opposite of each other is particularly worthy of note. That an elevated measurement of AST is associated with an increasing alcohol consumption even at older ages may suggest continued damage or sustained damage following earlier damage caused by consistently high levels of alcohol consumption.

The finding of elevated bilirubin to be so strongly associated with being male is also worth consideration. It is possible that there is a much higher prevalence of Gilbert's syndrome among men although I could not examine this within these data.

The LFTs that I have studied may not actually be markers of liver function (as discussed in section 1.4.2). Indeed the observed associations with other comorbid conditions, particularly diabetes, might suggest that these enzymes are produced in more significant amounts in the presence of other diseases.

It is possible that diabetes is a marker of undiagnosed (or non-recorded) non-alcoholic fatty liver disease or other underlying syndromes that may be the precursor of liver disease.

9 Mortality associated with elevated liver function tests

9.1 Introduction

This study aims to determine the health consequences in people aged over 75 with elevated liver function tests, in terms of the risk of all cause and cause-specific mortality.

9.2 Methods

9.2.1 Dataset used

The data used in this study are those from the detailed nurse assessment contained within the 'detail' database as well as information taken from the 'deaths' and 'censoring' databases (See Figure 6-2). A total of 15,308 participants aged 75 and over are included in the subsequent analyses. The definition of elevated liver function is as described in section 7.2.3.1 following imputation of missing upper limits using the median reference ranges.

9.2.2 Additional definitions

9.2.2.1 Cause of death

Deaths were coded according to the International Classification for Diseases, 9th revision (ICD9) until September 2002, and according to the 10th revision (ICD10) afterwards. I specifically examined causes of death that are most common in patients of this age group,[117] namely from cardiovascular disease (ICD9 401-405, 410-414, 425-447; ICD10 I10-I15, I20-I25, I42-I52, I6-I77, I79), cancer (all cancers excluding liver cancer (ICD9 140-154, 156-239;

ICD10 C0-C21, C23-D4)), respiratory disease (ICD9 46-51; ICD10 J). I was additionally interested in mortality from liver disease (viral hepatitis, liver cancer and liver disease (ICD9 070, 155, 570-573; ICD10 B15-B19, C22, K7)). Participants were assigned cause of death based on the underlying cause of death as given by the NHSCR.

9.2.3 Statistical analysis

Subjects were considered as contributing time to the analysis from the date of interview until death, censoring (migration) or 5 November 2005 (the last date of available data from the ONS) whichever came earliest. Associations between death and demographic, lifestyle and medical characteristics were examined in a control population consisting of all those people without any LFT abnormality in order to identify appropriate confounding variables. All cause and cause-specific mortality were examined for each elevated LFT in turn. Cox proportional hazards regression analysis was used to compare the survival of cohorts with normal and elevated LFTs. Analysis was performed treating an individual practice as a clustered unit. A priori confounders of age, sex and co-morbidity as well as other confounders identified in Section 8.3 for individual LFTs were included within multivariate cox proportional hazards models to provide adjusted hazard ratios. Proportional hazards assumptions were checked using Schoenfeld residuals and log-log plots.

9.3 Results

9.3.1 Mortality of whole population

Of the 15,308 participants in this study, 9268(60.5%) had died by 5 November 2005 (see Table 9-1). Deaths from cardiovascular disease, cancer and respiratory disease accounted for 7200 (77.7%) of all deaths in this population. Only 52 (0.6%) participants were recorded as having died from liver disease.

Table 9-1 Selected causes of death

Cause of death	N	% (of total deaths)
Total deaths	**9268**	**100**
Cancer	1715	18.5
CVD	3912	42.2
Respiratory	1573	17.0
Liver	52	0.6
All other	1999	21.6
Missing	17	0.2
Alive	**6040**	

9.3.2 Associations between death and demographic, lifestyle and clinical characteristics

Examining the population of participants with no elevated LFTs revealed significant associations between sex, age, smoking status, BMI, WHR and comorbidity and risk of death on univariable analysis (see Table 9-2). There was a decreased risk of death associated with being female and increasing BMI for increase in BMI category) but an increased risk of death associated with increasing age, being a smoker (current or ex-), increasing WHR and increasing comorbidity score. All individual comorbidities examined showed an increased risk of death, bar cancer and hypertension. There was no statistically significant association between increasing alcohol consumption and death.

Multivariable analysis included sex, age, smoking status, WHR and comorbidity score with all variables remaining statistically significantly associated with death upon mutual adjustment.

Table 9-2 Association between demographic, lifestyle and clinical factors and death in population with no elevated liver function test

	Alive (N=4227)		Dead (N=5798)		OR [95% CI]	OR [95% CI]
	N	%	N	%	Univariable	Multivariable
Sex						
Female	2841	67.2	3381	58.3	0.67 [0.61, 0.72]	0.62 [0.55, 0.70]
Male	1386	32.8	2417	41.7		
Age						
Median age [IQR] (range)						
Age group (fine)						
75-	539	12.7	352	6.1		
76-	766	18.1	517	8.9		
77-	629	14.9	450	7.7.		
78-	408	9.7	376	6.5		
79-	350	8.3	400	6.9		
80-	326	7.7	406	7.0		
81-	306	7.2	406	7.0		
82-	234	5.5	382	6.6		
83-	166	3.9	403	7.0		
84-	148	3.5	350	6.0		
85-	97	2.3	323	5.6		
86-	78	1.9	292	5.0		
87-	61	1.4	255	4.4		
88-	44	1.0	224	3.9		
89-	23	0.5	175	3.0		
90+	31	0.7	463	8.0		
Missing	21	0.5	24	0.4		
Odds ratio for yearly increase in age					1.20 [1.18, 1.21]	1.22 [1.20, 1.23]
Alcohol						
Median units of alcohol intake in past week						
Alcohol units						
0	1490	35.3	2104	36.3		
1-	1640	38.8	1919	33.1		
8-	309	7.3	383	6.6		
15-	92	2.2	114	2.0		
22+	58	1.4	104	1.8		
Missing	638	15.0	1174	20.2		
Odds ratio for increase in alcohol group					0.95 [0.91, 1.01]	-
Smoking						
Never	1743	41.2	2074	35.8		
Ex	2070	49.0	2854	49.2	1.16 [1.06, 1.26]	1.18 [1.06, 1.31]
Current	301	7.1	685	11.8	1.88 [1.61, 2.18]	2.42 [2.04, 2.87]
Missing	113	2.7	185	3.2		
BMI group						

<18.5	49	1.2	156	2.7	2.16 [1.56, 3.01]	
18.5-	1505	35.6	2152	37.1	-	
25-	1837	14.5	1998	34.5	0.76 [0.69, 0.83]	
30-	543	12.9	679	11.7	0.87 [0.76, 0.99]	
35+	124	2.9	132	2.3	0.72 [0.56, 0.93]	
Missing	169	4.0	681	11.8		
Odds ratio for increase in BMI group					0.86 [0.82, 0.91]	
Waist:hip						
0.65-0.74	174	4.1	157	2.7	0.87 [0.69, 1.10]	
0.75-0.84	1580	37.4	1638	28.3	-	
0.85-0.94	1573	37.2	2253	38.9	1.42 [1.29, 1.56]	
0.95-1.04	665	15.7	1047	18.1	1.59 [1.41, 1.80]	
1.05-1.15	52	1.2	110	1.9	2.20 [1.56, 3.09]	
Missing	183	4.3	593	10.2		
				Trend	1.28 [1.21, 1.34]	1.08 [1.01, 1.16]
Presence of Co-morbidity						
Diabetes	219	5.2	530	9.1	1.85 [1.57, 2.19]	
Heart attack	303	7.2	741	12.8	1.89 [1.64, 2.18]	
Hypertension	1406	33.3	1925	33.2	1.02 [0.93, 1.11]	
Stroke	196	4.6	684	11.8	2.74 [2.32, 3.23]	
Cancer	419	9.9	616	10.6	1.09 [0.95, 1.24]	
Ulcer	468	11.1	734	12.7	1.14 [1.01, 1.29]	
Angina	236	5.6	393	6.8	1.21 [1.02, 1.44]	
Dementia	5	0.1	56	1.0	7.86 [3.14, 19.7]	
Co-morbidity score						
0	1677	39.7	1813	32.3		
1	1635	38.7	2114	36.5	1.20 [1.09, 1.31]	
2	648	15.3	1171	20.2	1.68 [1.49, 1.89]	
3+	224	5.3	583	10.0	2.43 [2.05, 2.88]	
Odds ratio for increase in co-morbidity score					1.32 [1.26, 1.38]	1.39 [1.32, 1.46]

*adjusted for age, sex, smoking, WHR and comorbidity score.

9.3.3 Mortality associated with elevated AST

Mortality in subjects with an elevated AST was 104.8 per 1000 person-years representing an increase of 10 deaths per 1000 person-years of follow-up compared to subjects with a normal AST (see Table 9-3). This corresponded to an adjusted hazard ratio of 1.27, i.e. an elevated AST was associated with a 27% (95% CI [9%, 47%]) increased hazard for all-cause mortality. This is displayed visually in the Kaplan-Meier plot (see Figure 9-1). There was an increased hazard of death observed with increasing levels of abnormality with patients, with an elevated AST over 2 times the ULN having a 62% increased hazard of death.

An elevated AST was associated with an increase in mortality from cancer (56% increased hazard) and mortality from liver disease (7-fold increased hazard) (see Table 9-3). It should be noted that only 8 out of 429 subjects (1.8%) with an elevated AST died from liver disease.

Examining the Schoenfeld residuals and log-log plots gave no evidence of invalidation of the proportional hazards assumption (see Figure 9-2 and Figure 9-3).

Table 9-3 Cox proportional hazards model for death (all-cause and cause-specific mortality) by AST test

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
All-cause mortality					
Normal AST	7319	77485	94.5	-	
Elevated AST	271	2586	104.8	1.11 [0.99, 1.26]	1.27 [1.09, 1.47]
Elevated AST within 1x	229	2267	101.0	1.07 [0.92, 1.24]	1.17 [1.02, 1.34]
Elevated AST over 2x	42	319	131.7	1.43 [1.04, 1.96]	1.62 [1.22, 2.16]
Hazard ratio for increase in AST abnormality group				1.12 [1.02, 1.24]	1.26 [1.12, 1.41]
Cause-specific mortality					
CVD					
Normal AST	3097	77485	40.0	-	
Elevated AST	109	2586	42.1	1.06 [0.87, 1.28]	1.15 [0.92, 1.44]
Cancer (excluding liver cancer)					
Normal AST	1359	77485	17.5	-	
Elevated AST	63	2586	24.4	1.40 [1.09, 1.80]	1.56 [1.21, 2.01]
Respiratory disease					
Normal AST	1235	77485	15.9	-	
Elevated AST	33	2586	12.7	0.80 [0.57, 1.13]	1.03 [0.70, 1.52]
Liver disease					
Normal AST	38	77485	0.49	-	
Elevated AST	8	2586	3.09	6.28 [2.92, 13.5]	7.00 [2.88, 17.06]

*adjusted for age, sex, comorbidity group, alcohol intake and WHR group.

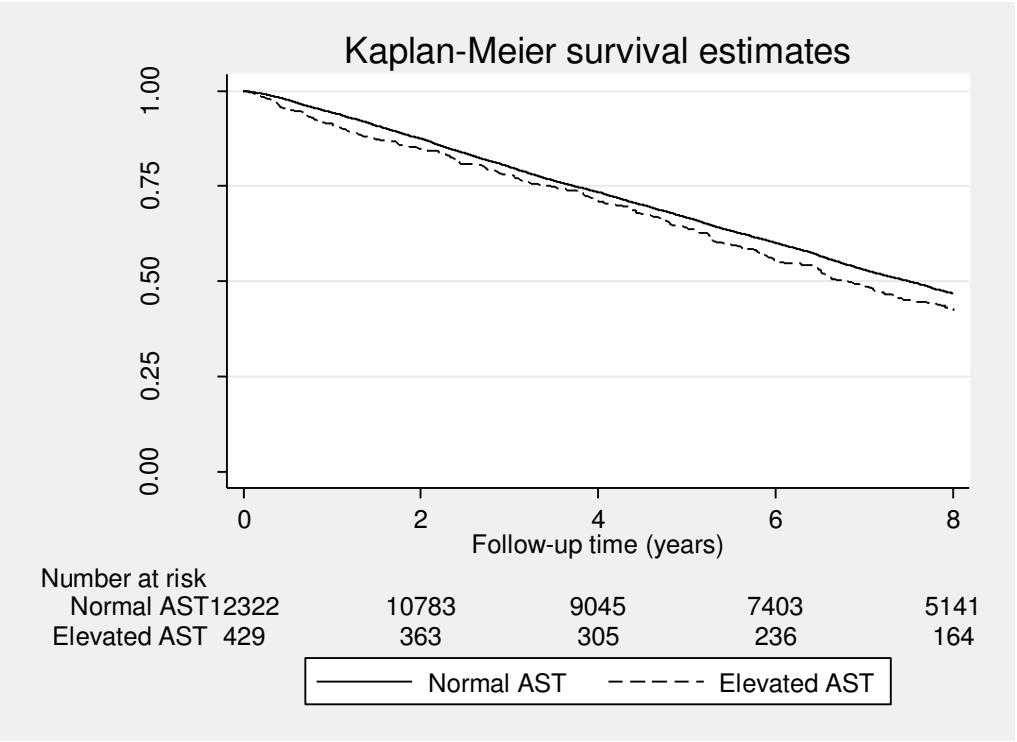


Figure 9-1 Kaplan-Meier survival estimates for all-cause mortality for AST measurement

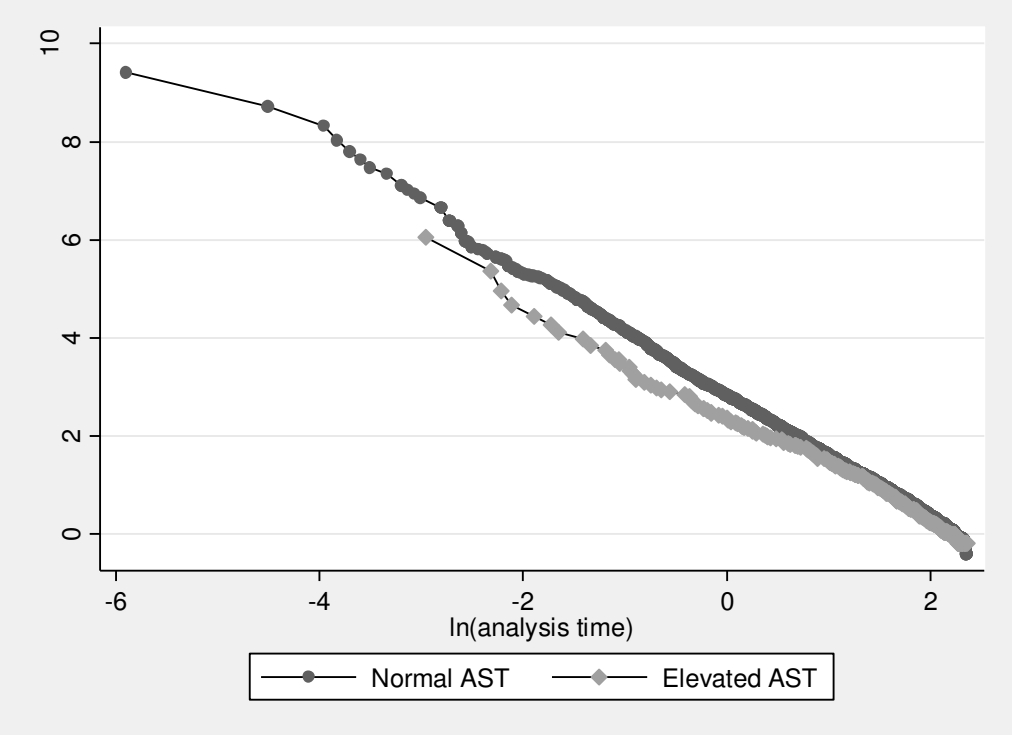


Figure 9-2 Log-log plot for all-cause mortality for AST measurement

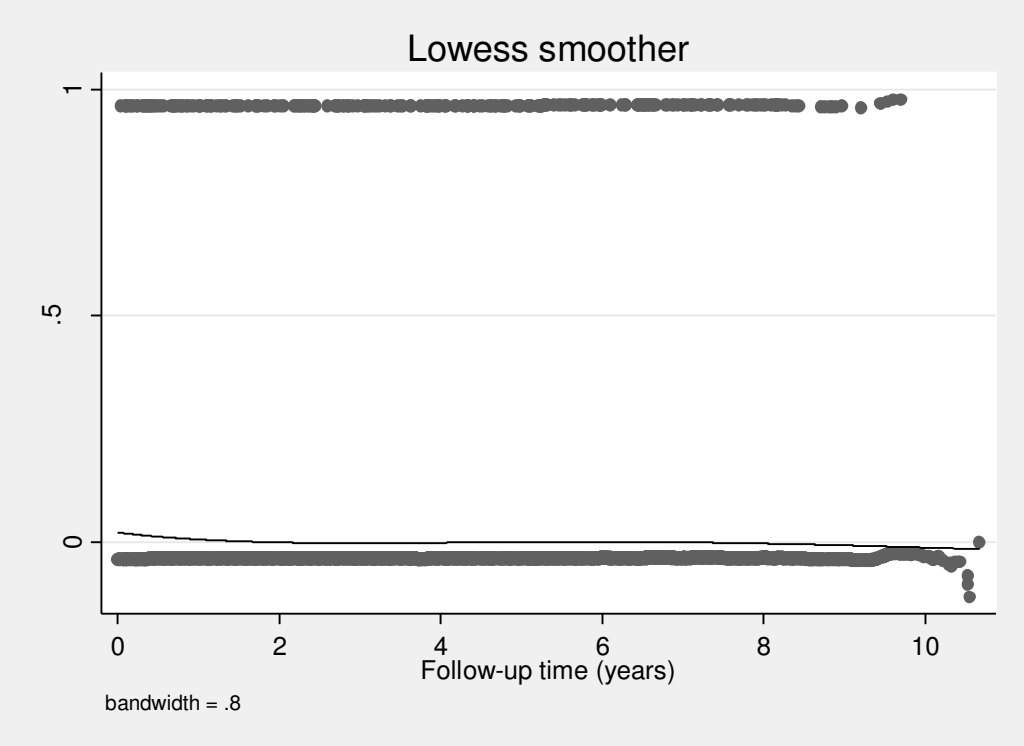


Figure 9-3 Schoenfeld residuals against time for all-cause mortality for measurement of AST

9.3.4 Mortality associated with elevated ALP

Mortality in subjects with an elevated ALP was 138.8 per 1000 person-years of follow-up representing an increase of nearly 50 deaths per 1000 person years compared with subjects with a normal ALP measurement (see Table 9-4). An elevated ALP measurement was associated with a 47% increase in hazard of death, adjusted for age, sex, co-morbidity score and alcohol intake (hazard ratio 1.47; 95% CI [1.35, 1.61]). This higher hazard of death is shown graphically in the Kaplan-Meier plot (see Figure 9-4).

An elevated ALP was associated with an increased hazard for death from CVD (34% increase), death from cancer (61% increase), death from respiratory disease (58% increase) and death from liver disease (nearly 6-fold increase) (see Table 9-4). However, only 13 out of 1246 subjects (1.0%) with an elevated ALP died from liver disease.

Examining the Schoenfeld residuals and log-log plots gave no evidence of invalidation of the proportional hazards assumption (see Figure 9-5 and Figure 9-6).

Table 9-4 Cox proportional hazards model for death (all-cause and cause-specific mortality) by ALP test

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
All-cause mortality					
Normal ALP	7068	77752	90.9	-	
Elevated ALP	903	6503.9	138.8	1.58 [1.47, 1.69]	1.47 [1.35, 1.61]
Elevated ALP within 1x	809	5895.7	137.2	1.56 [1.44, 1.68]	1.42 [1.32, 1.52]
Elevated ALP over 2x	94	608.3	154.5	1.76 [1.44, 1.68]	1.44 [1.13, 1.84]
Hazard ratio for increase in ALP abnormality group				1.47 [1.39, 1.56]	1.37 [1.26, 1.48]
Cause-specific mortality					
Cardiovascular disease					
Normal ALP	3010	77752	38.7	-	
Elevated ALP	358	6504	55.0	1.46 [1.30, 1.62]	1.34 [1.17, 1.55]
Cancer (excluding liver cancer)					
Normal ALP	1324	77752	17.0	-	
Elevated ALP	174	6504	26.8	1.61 [1.37, 1.89]	1.61 [1.39, 1.86]
Respiratory disease					
Normal ALP	1181	77752	15.2	-	
Elevated ALP	161	6504	24.8	1.68 [1.42, 1.98]	1.58 [1.32, 1.90]
Liver disease					
Normal ALP	35	77752	0.45	-	
Elevated ALP	13	6503.9	2.00	4.59 [2.43, 8.69]	5.95 [2.83, 12.51]

*adjusted for age, sex, comorbidity group and alcohol intake

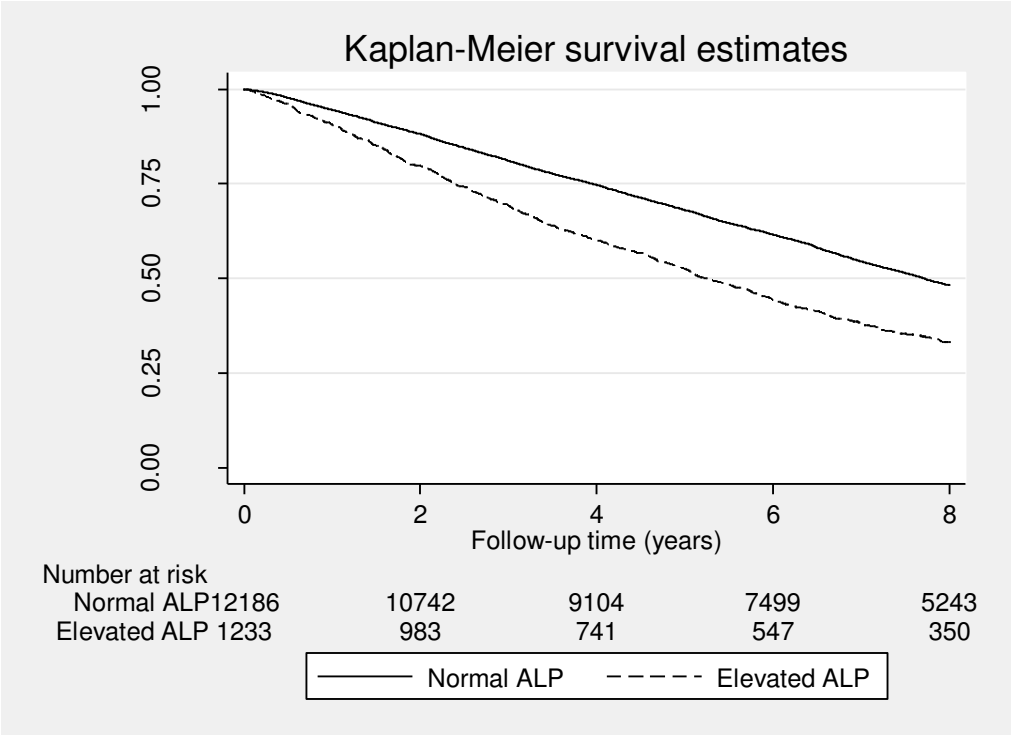


Figure 9-4 Kaplan-Meier survival estimates for all-cause mortality for ALP measurement

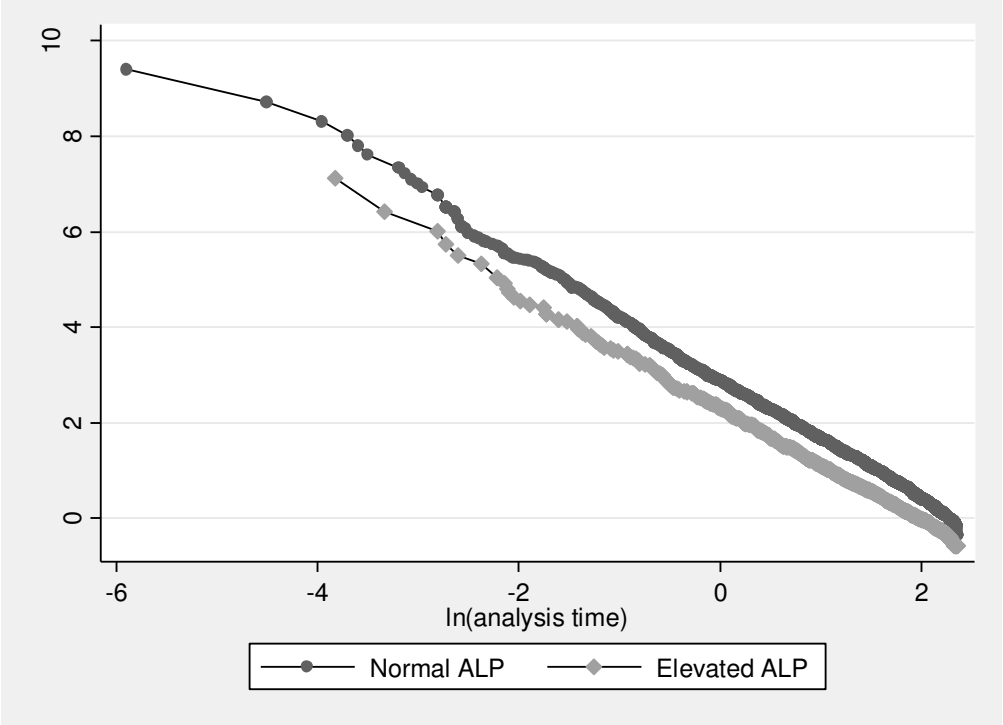


Figure 9-5 Log-log plot for all-cause mortality for ALP measurement

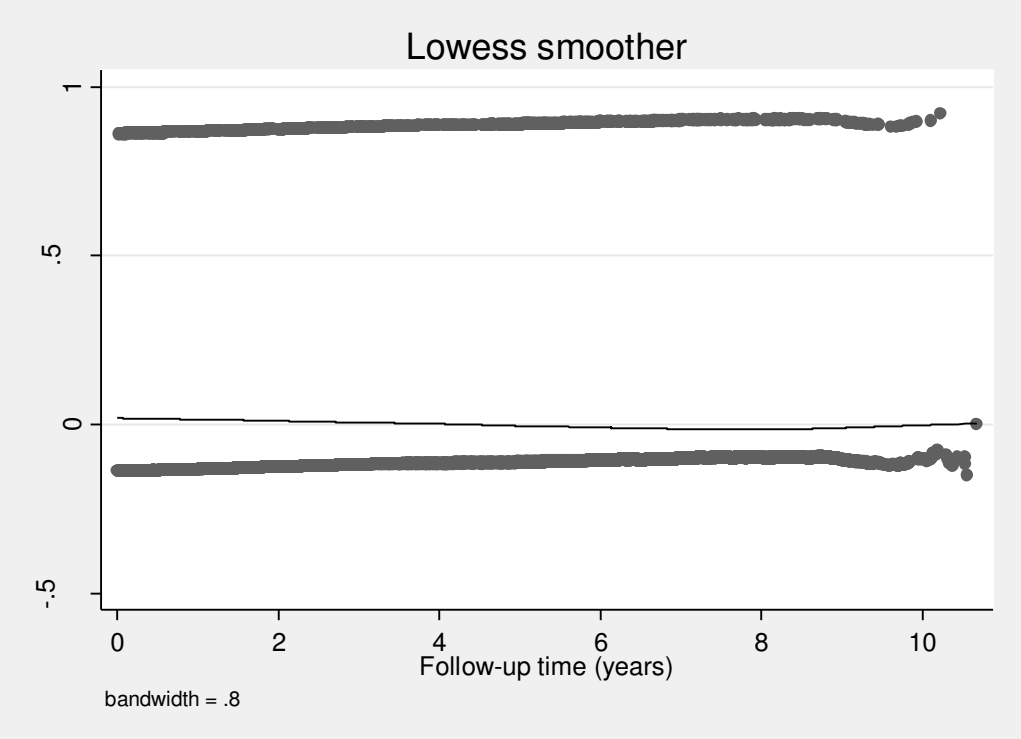


Figure 9-6 Schoenfeld residuals against time for all-cause mortality for measurement of ALP

9.3.5 Mortality associated with elevated bilirubin

Elevated bilirubin was associated with a small increase in hazard of death (15%, 95%CI [2%, 30%]) following adjustment for the confounding factors of age, sex, comorbidity score, smoking status, alcohol consumption and WHR group (see Table 9-5). This slight increase in hazard of death is shown graphically in the Kaplan-Meier plot (see Figure 9-10).

Elevated bilirubin was not associated with a change in hazard of any cause-specific mortality examined (see Table 9-5).

Examining the Schoenfeld residuals and log-log plots gave no evidence of invalidation of the proportional hazards assumption (see Figure 9-8 and Figure 9-9).

Table 9-5 Cox proportional hazards model for death (all-cause and cause-specific mortality) by bilirubin test

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
All-cause mortality					
Normal Bilirubin	7063	75176	94.0	-	
Elevated Bilirubin	416	4109	101.2	1.09 [0.99, 1.20]	1.15 [1.02, 1.30]
Elevated bilirubin within 1x	388	3866	100.4	1.08 [0.98, 1.19]	1.14 [0.99, 1.29]
Elevated bilirubin over 2x	28	243	115.3	1.24 [0.86, 1.79]	1.35 [0.91, 2.00]
Hazard ratio for increase in bilirubin abnormality group				1.09 [1.00, 1.18]	1.07 [0.98, 1.17]
Cause-specific mortality					
Cardiovascular disease					
Normal Bilirubin	2981	75176	39.7	-	
Elevated Bilirubin	190	4109	46.2	1.18 [1.02, 1.36]	1.15 [0.98, 1.36]
Cancer (excluding liver cancer)					
Normal Bilirubin	1331	75176	17.7	-	
Elevated Bilirubin	69	4109	16.8	0.96 [0.75, 1.22]	0.90 [0.68, 1.19]
Respiratory disease					
Normal Bilirubin	1203	75176	16.0	-	
Elevated Bilirubin	58	4109	14.1	0.89 [0.68, 1.16]	0.97 [0.69, 1.35]
Liver disease					
Normal Bilirubin	44	75176	0.6		
Elevated Bilirubin	5	4109	1.22	2.11 [0.84, 5.32]	1.71 [0.63, 4.65]

*adjusted for age, sex, comorbidity group, alcohol intake, smoking status and WHR group.

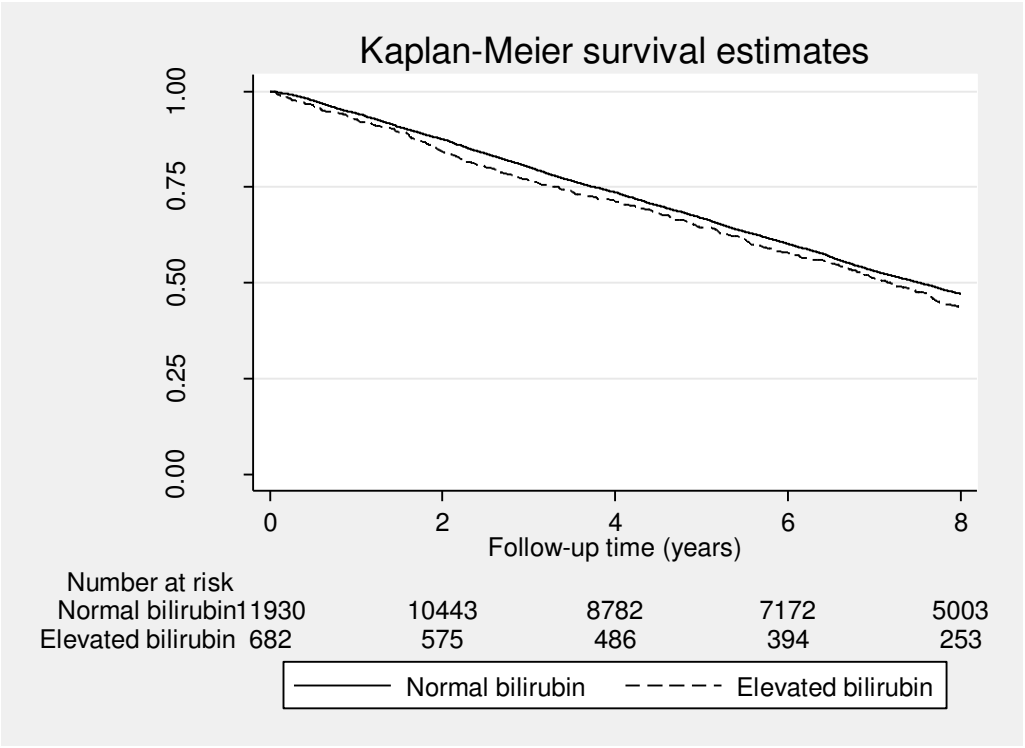


Figure 9-7 Kaplan-Meier survival estimates for all-cause mortality for bilirubin measurement

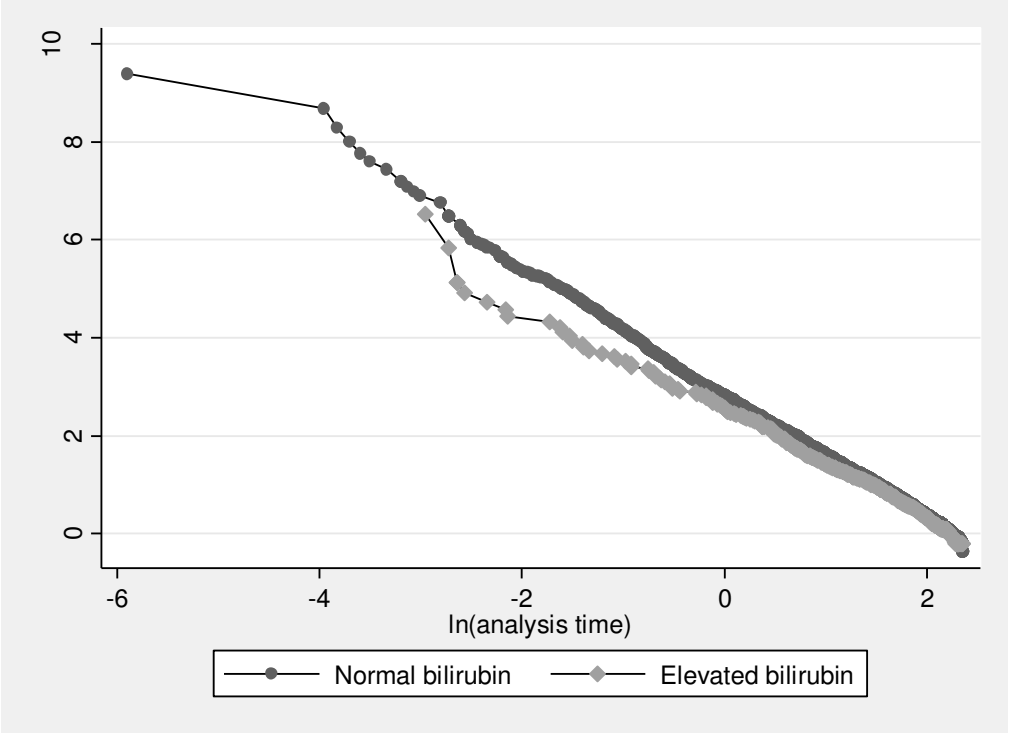


Figure 9-8 Log-log plot for all-cause mortality for bilirubin measurement

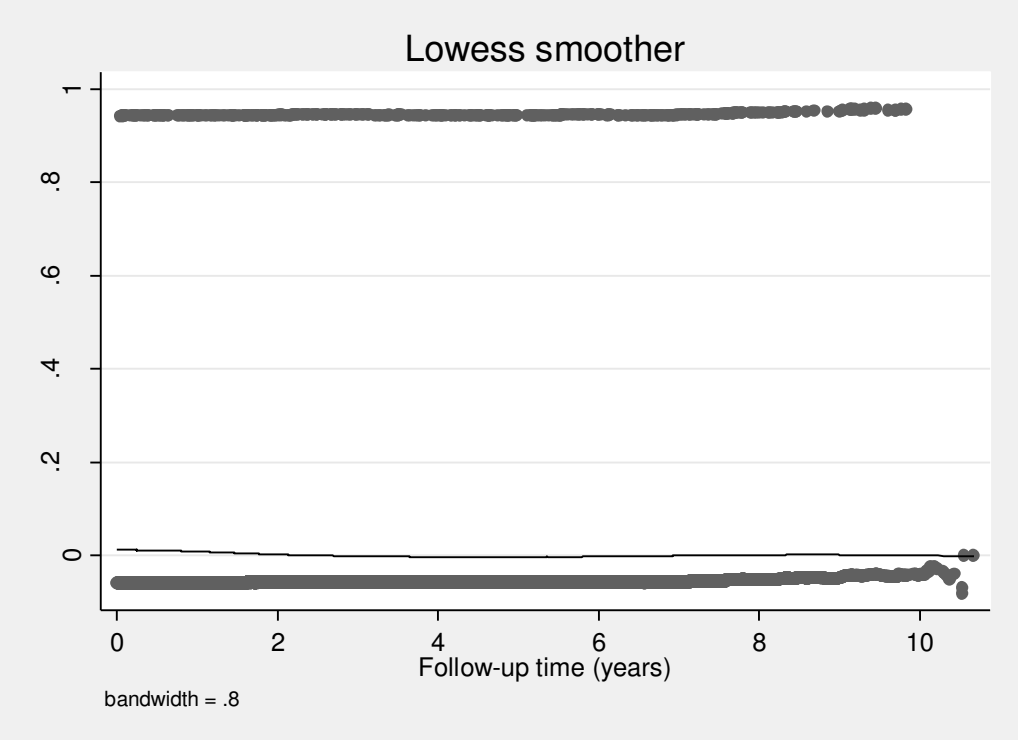


Figure 9-9 Schoenfeld residuals against time for all-cause mortality for measurement of bilirubin

9.3.6 Mortality associated with any elevated LFT

Mortality in subjects with any elevated LFT was 118.4 per 1000 person-years representing an increase of nearly 18 deaths per 1000 person-years of follow-up compared to subjects with all normal LFTs (see Table 9-6). This corresponded to an adjusted hazard ratio of 1.27, i.e. any elevated LFT was associated with a 27% (95% CI [19%, 36%]) increased hazard for all-cause mortality. This is displayed visually in the Kaplan-Meier plot (see Figure 9-10). Any elevated LFT was associated with an increase in mortality from all the specific causes that were examined. For deaths from cardiovascular disease a 27% increased hazard was seen, death from cancer a 23% increased hazard, death from respiratory disease a 21% increased hazard and a 3-fold hazard of death from liver disease (see Table 9-6). There was less than 1 excess death from liver disease per 1000 person years for persons with any abnormal LFT compared with those with all normal LFTs.

Examining the Schoenfeld residuals and log-log plots gave no evidence of invalidation of the proportional hazards assumption (see Figure 9-11 and Figure 9-12).

Table 9-6 Cox proportional hazards model for death (all-cause and cause-specific mortality) for any elevated LFT

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
All-cause mortality					
Normal	6556	72,320	90.7		
Elevated	1447	12,217	118.4	1.33 [1.26, 1.41]	1.27 [1.19, 1.36]
Cause-specific mortality					
Cardiovascular disease					
Normal	2768	72,320	38.3		
Elevated	611	12,217	50.0	1.33 [1.22, 1.45]	1.27 [1.16, 1.39]
Cancer (excluding liver cancer)					
Normal	1240	72,30	17.1		
Elevated	266	12,217	21.8	1.29 [1.13, 1.47]	1.23 [1.10, 1.39]
Respiratory disease					
Normal	1112	72,30	15.4		
Elevated	234	12,217	19.2	1.27 [1.10, 1.46]	1.21 [1.02, 1.42]
Liver disease					
Normal	32	72,30	0.44		
Elevated	17	12,217	1.39	3.22 [1.79, 5.79]	3.11 [1.74, 5.54]

*adjusted for sex, age and comorbidity group

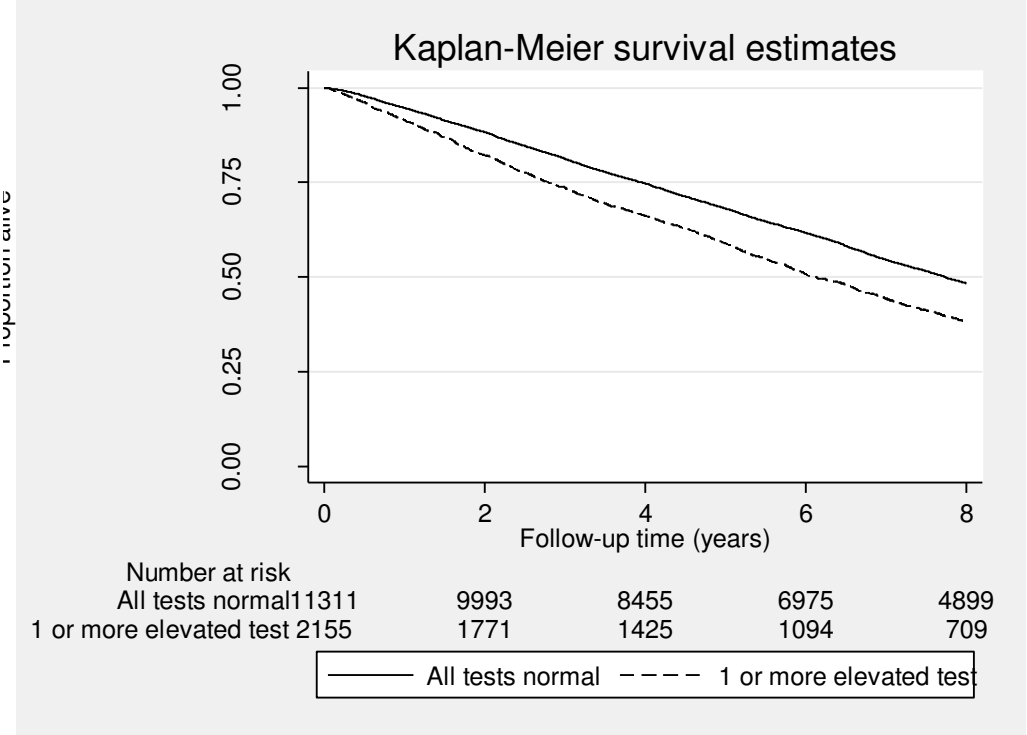


Figure 9-10 Kaplan-Meier survival estimates for all normal LFTs vs. any elevated LFT

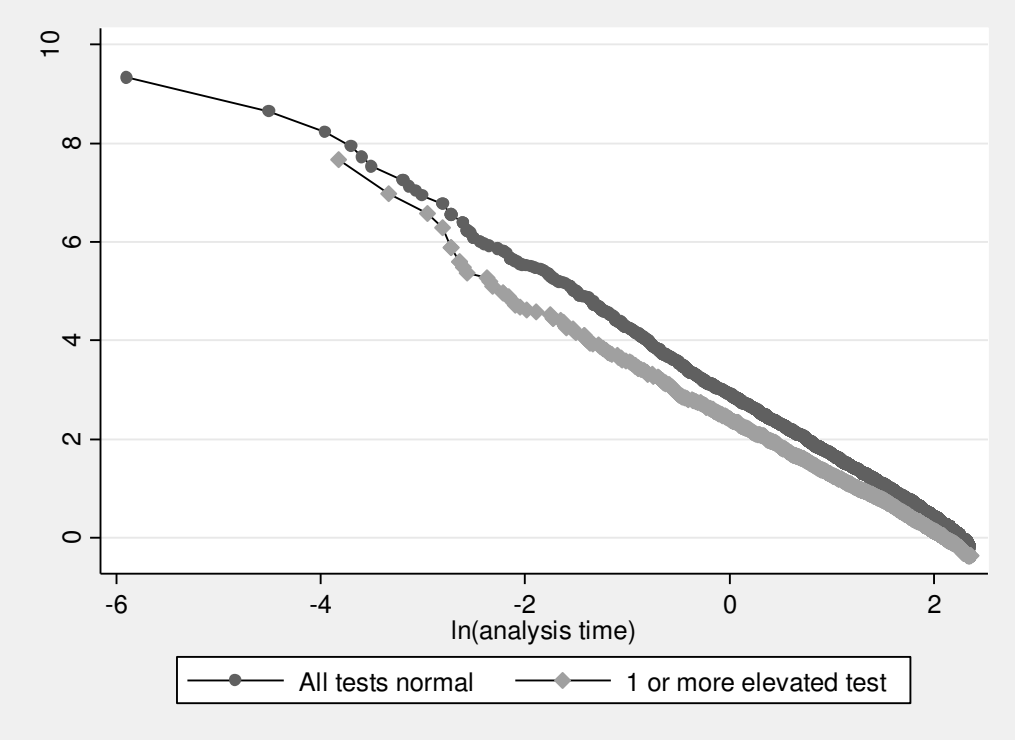


Figure 9-11 Log-log plot for all-cause mortality for any elevated LFT measurement

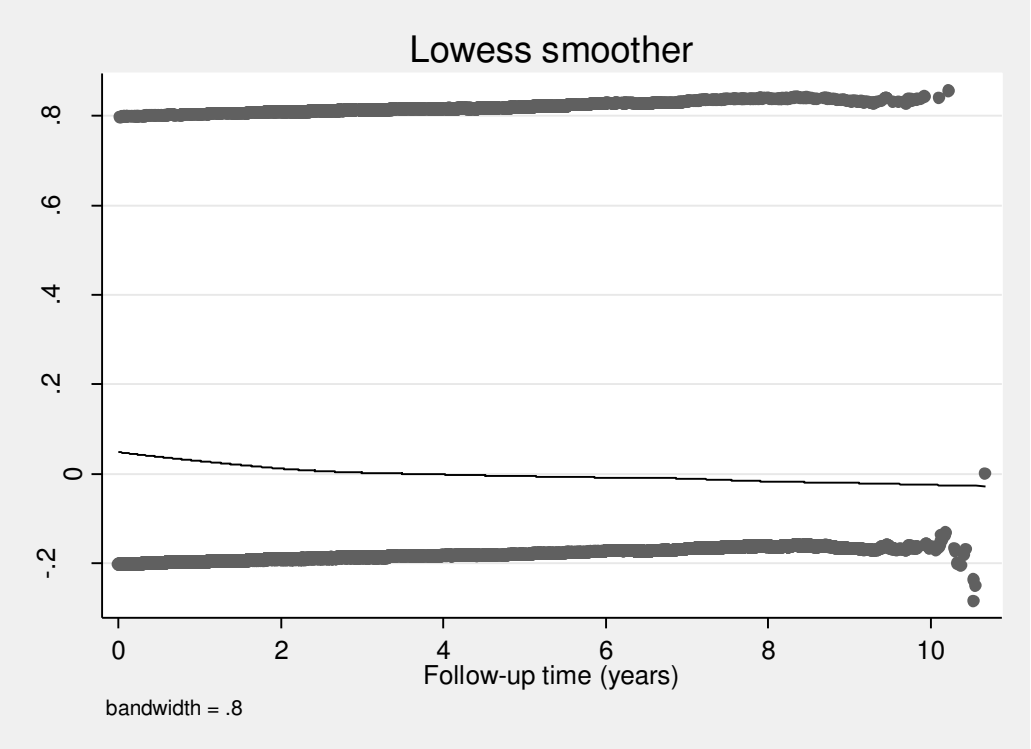


Figure 9-12 Schoenfeld residuals against time for all-cause mortality for any elevated LFT measurement

9.4 Discussion

9.4.1 Key findings

A single elevated liver function test was associated with a higher risk of death overall, and for AST and ALP in particular a higher risk of death from liver disease, compared to those with normal liver function tests.

9.4.2 Strengths and limitations

In this study I was able to assess the association of certain liver function tests with subsequent mortality in a representative sample of all people aged 75 and over. Given that people of this age have such a high mortality and therefore there were a large number of events (deaths) I was able to perform survival analysis looking at both all-cause mortality and specific causes of death. This has enabled me to provide estimates of the association of elevated liver function test and cause-specific mortality which has not been previously available. In addition to an unsurprising increased risk of death from liver disease (albeit mediated through very small absolute numbers of deaths) both elevated AST and ALP were seen to be associated with an increased risk of death from cancer (excluding liver cancer). Elevated ALP was also associated with an increased risk of the other two specific causes of death examined, cardiovascular disease and respiratory disease. Rather than being related to liver function per se, this may reflect the fact that these enzymes are also present in other body tissues, not just specific to the liver. As previously discussed it is arguable that abnormalities of AST, ALP and bilirubin are of secondary importance when looking at liver function compared with a measurement of alanine aminotransferase (ALT) which is specific to the

liver. I was unable to investigate this as a blood test for this enzyme was not a part of the original study design.

9.4.3 Comparison with previously published work

Although I was unable to exclude people with previously diagnosed liver disease, the representative nature of this study enables me to provide a possibly more accurate estimate of the association of elevated liver function tests in the general population with mortality than has been previously available.[66 76] A higher risk of death was seen with increasingly abnormal results in both these studies as with my data. These previous studies, by virtue of the method of data collection, will have introduced an inherent selection bias to their study populations as to which people within the geographic area had a recorded measurement of liver function, most likely to lead to an overestimate of the association between elevated liver function and mortality. Indeed the estimates of mortality associated with transaminases and ALP in the population from Scotland are slightly higher than those reported in this chapter.[66] Further studies from working populations in Germany and South Korea also report greater increases in hazard of all-cause mortality than those shown in my data.[68 75]

I identified one study that specifically looked at the association between liver function and mortality in the elderly, which came from a small population of 70 year-olds in Jerusalem.[77] This study did not show any significant associations between either AST or ALP and all-cause mortality. However, the categorisation of liver function as above or below the mean value in the study population makes the interpretation of these results difficult to compare with

my study where I was specifically looking at abnormalities as defined by upper limits of normal reference ranges.

9.4.4 Conclusions

This study has shown that although abnormalities in liver function are fairly common they are associated with only a modest increased risk in all-cause mortality in the elderly population.

The findings of an association between elevated liver function tests and mortality from cardiovascular disease, cancer, respiratory disease as well as liver disease, independent of comorbidity, suggest that rather than simply a marker of liver function the investigation of people with elevated LFTs, particularly those greater than 2 x the ULN, may lead to the identification of potentially treatable conditions that underlie death. However, by comparison the simply derived comorbidity score exhibited a stronger relationship with death than any of the LFTs examined.

A recent report from Department of Health Quality Strategy Team on Liver Disease called for guidance to be made available to general practitioners on the use and interpretation of liver function tests.[9] I await the results of two HTA funded studies which may provide additional recommendations for the management of elevated liver function tests.[118] [119]

It will be particularly important to evaluate the use of liver function tests and subsequent referrals in this growing sector of the population of the UK,[120] those aged 75 and over, where incidental findings, and therefore potentially costly and avoidable referral and follow-up, are even more likely owing to

prescribing practices (as discussed in section 7.4.4). What action needs to be taken on obtaining a single elevated liver function test in this group of older people remains open to debate and further study. Though two studies have shown that underlying liver disease was present in the majority of people who presented with elevated liver function tests but were otherwise asymptomatic for liver disease and did not have a history of drug or alcohol problems[121 122] it would seem that, in the absence of any evidence for any overwhelming increases in mortality following a single elevated measurement of liver function, current practise of referral and active investigation of patients only with persistent abnormalities should be continued.

10 Conclusions

10.1 Overall findings

In describing some aspects of the epidemiology of cirrhosis and liver function this thesis has addressed, in part, the burden of liver disease in the UK as highlighted in the four areas discussed in section 1.1.

1. I have considered the frequency of liver disease through examination of the incidence and prevalence of cirrhosis and the frequency of potentially undiagnosed liver disease through examination of the prevalence of abnormal liver function tests in a group of people aged 75 and over.
2. I have considered the mortality from liver disease through examination of mortality subsequent to a diagnosis of cirrhosis and subsequent to a single elevated LFT measurement.
3. I have considered the morbidity associated with liver disease through examination of the progression of cirrhosis using recognised clinical sequelae including an estimate of the rate of decompensation.
4. Although I have not attempted to consider the financial or service requirements associated with liver disease through any formal mechanisms the measures described above will of themselves be useful in the modelling and cost-effectiveness analyses that could be undertaken to look at the burden of liver disease in the UK. I have also applied my results to recent UK population figures to provide an estimate of the annual number of new cases of cirrhosis, the total number of people living with cirrhosis and the number of older people who might be expected to have one or more abnormal LFTs.

10.2 Suggestions for further research

Epidemiology of cirrhosis

The data used in chapters 3 through 5 were extracted from the GPRD in April 2002. Recently (2009) the GPRD has established formal data links with the HES data and with the ONS vital statistics database of death registrations. Using a more recent extraction of data it should be possible

a) to explore if the increasing trend in incidence of cirrhosis has continued throughout the last decade,
b) to examine the cause of death of patients with cirrhosis compared with the general population (available in new GPRD data extractions), and
c) to describe the progression of cirrhosis using information contained within linked hospital data, including additional clinical sequelae and commonly used prognostic scores through the availability of laboratory data (again, available in new GPRD data extractions).

In addition, it is probable that a diagnosis of cirrhosis is associated with other sequelae that have not been addressed in this thesis. Of particular interest clinically is the occurrence of hepatocellular carcinoma. Further exploration of readily available data would inform the current practices for surveillance of hepatocellular carcinoma and potentially identify both high and low risk groups in which to either target or stop surveillance.

Epidemiology of liver function

I have described the epidemiology of elevated liver function in a particular group of the population, those aged 75 and above. It would be interesting to obtain data from cohorts of people of younger age groups to observe

a) the absolute proportion of people who had elevated liver function, and
b) whether similar associations between clinical, demographic and lifestyle factors and mortality exist at other ages

As elevated AST and ALP were both associated with deaths from cancer it would be interesting to examine whether these elevated LFTs were also associated with the incidence of cancer. This should be possible using the same "MRC Elderly" dataset as this has been linked to the national cancer registry.

The utility of a single measurement of elevated liver function remains questionable and it would be worthwhile to try to obtain data on patients who had had repeated measures of liver function to see if persistently elevated LFTs were more strongly associated with mortality, as would probably be expected.

10.3 Overall conclusion

This thesis has described the increasing incidence of cirrhosis in the UK over the period 1992-2001 and the considerable excess mortality and rapid progression associated with a diagnosis of cirrhosis.

As cirrhosis probably represents the end stage of many chronic liver diseases it is perhaps now of even greater importance to consider the aetiologic factors that lead to the acquisition of cirrhosis and consider measures to reduce the occurrence of these liver diseases and eventually cirrhosis.

Elevated liver function tests appear to be associated with more than just liver disease. It will be important to consider how these tests should in future be used – more widely as a measure of general health or targeted more specifically. The necessity of accurate estimates of the prevalence of elevated LFTs and their associations will be paramount to any changes in the current practices of investigation and referral.

11 References

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Appendix I Papers published from the work in this thesis

Fleming KM, Aithal GP, Solaymani-Dodaran M, Card T, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: A general population-based study. *J Hepatol* 2008 49(5):732-8

Appendix II Abstracts presented at conferences based on work in this thesis

Oral presentations

- United European Gastroenterology Week. Oral presentation: Updated estimates of the 1-year progression of disease following diagnosis of cirrhosis.

- British Association for Studies of the Liver Annual meeting, September 2007. Plenary presentation: Incidence of cirrhosis in the UK, 1992-2001: a population-based study.

Poster presentations

- Updated estimates of the 1-year progression of disease following diagnosis of cirrhosis. BASL, Sept 2008.

- Incidence of cirrhosis in the UK, 1992-2001: a population-based study. AASLD, Nov 2007; UEGW, Oct 2007 (prize for best poster awarded).

Appendix III Code lists

Appendix III-a Codes for liver disease

description	medcode
TYPHOIDAL HEPATITIS	001 C
AMOEBIC ABSCESS LIVER	0060B
HEPATITIS AMOEBIC	0060BH
AMOEBIC ABSCESS BRAIN & LIVER	0060C
AMOEBIC ABSCESS LUNG & LIVER	0060D
AMOEBIC ABSCESS SPLEEN & LIVER	0060E
TUBERCULOUS HEPATITIS	014 H
TULARAEMIA HEPATITIS	021 H
HEPATITIS BRUCELLOSIS	0239H
LEPROTIC HEPATITIS	0309H
PNEUMOCOCCAL HEPATITIS	0382H
HEPATITIS GAS GANGRENE	0390H
HERPES VIRUS HEPATITIS	054 H
RUBELLA HEPATITIS	056 H
YELLOW FEVER HEPATITIS	0609H
INFECTIOUS HEPATITIS	70
VIRUS HEPATITIS TYPE A	070 A
HEPATITIS C	070 AC
HEPATITIS TYPE C	070 AD
VIRUS HEPATITIS TYPE B	070 B
HEPATITIS CATARRHAL	070 C
HEPATITIS FULMINANT	070 F
HEPATITIS CHRONIC AGGRESSIVE	070 G
JAUNDICE CATARRHAL	070 JC
JAUNDICE EPIDEMIC	070 JE
JAUNDICE FEBRILE	070 JF
JAUNDICE INFECTIOUS	070 JN
HEPATITIS TYPE NON- A NON- B	070 N
HEPATITIS PERSISTENT CHRONIC	070 P
VIRUS HEPATITIS	070 RL
HEPATITIS COXSACKIE VIRUS	0749H
INFECTIOUS MONONUCLEOSIS HEPATITIS	075 H
HEPATITIS ADENOVIRUS	0788H
HEPATITIS CYTOMEGALIC INCLUSION VIRUS	0795H
Q FEVER HEPATITIS	0831H
MALARIAL HEPATITIS	0840H
SYPHILIS LIVER CONGENITAL	0900L
SYPHILIS LIVER ACQUIRED	095 L
HEPATITIS GONOCOCCAL	0988H
PERIHEPATITIS GONOCOCCAL	0988PH
SPIROCHAETAL HAEMORRHAGIC JAUNDICE	1000EJ
LEPTOSPIRAL HEPATITIS	1000H
JAUNDICE EPIDEMIC LEPTOSPIRAL	1000WL

JAUNDICE EPIDEMIC SPIROCHAETAL	1000WR
ACTINOMYCOSIS LIVER	113 L
COCCIDIOIDOMYCOSIS LIVER	114 L
HISTOPLASMOSIS LIVER	115 L
CRYPTOCOCCOSIS LIVER	1160CL
BLASTOMYCOSIS LIVER	1169L
SCHISTOSOMIASIS LIVER	1208L
CAT LIVER FLUKE INFECTION	1210C
CHINESE LIVER FLUKE DISEASE	1211CH
INFESTATION DISTOMA HEPATICUM	1213D
SHEEP LIVER FLUKE INFECTION	1213HF
HYDATID CYST LIVER	1220C
HYDATID CYST	1229C
FH: PORPHYRIA	1265
TOXOPLASMOSIS LIVER CONGENITAL	1302
SARCOIDOSIS	135
SARCOID	135 AA
SARCOID BOECK'S	135 BK
SARCOIDOSIS LIVER	135 L
SARCOIDOSIS PULMONARY	135 P
H/O: LIVER DISEASE	14C5.00
H/O: JAUNDICE	14C6.00
H/O: BILIARY DISEASE	14C7.00
H/O: GALLBLADDER DISEASE	14C7.11
H/O: LIVER RECIPIENT	14S8.00
MALIGNANT NEOPLASM LIVER	1550A
MALIGNANT NEOPLASM LIVER PRIMARY	1550AP
HEPATOMA	1550B
HAEMANGIOENDOTHELIAL SARCOMA LIVER	1550BH
SARCOMA LIVER PRIMARY	1550BP
CARCINOMA LIVER	1550C
HEPATOBLASTOMA	1550HB
MALIGNANT NEOPLASM HEPATOCELLULAR	1550HC
MALIGNANT CHOLANGIOMA	1551A
MALIGNANT NEOPLASM GALLBLADDER	1560A
CARCINOMA GALLBLADDER	1560C
MALIGNANT NEOPLASM EXTRAHEPATIC BILE DUC	1561A
CARCINOMA EXTRAHEPATIC BILE DUCT	1561C
MALIGNANT NEOPLASM AMPULLA OF VATER	1562A
CARCINOMA AMPULLA VATER	1562C
MALIGNANT NEOPLASM BILE/BILIARY TRACT	1569A
YELLOW/JAUNDICED COLOUR	1675
JAUNDICE - SYMPTOM	1675.11
BILIARY COLIC	1965
BILIARY COLIC SYMPTOM	1965.11
SECONDARY NEOPLASTIC DEPOSITS LIVER	1977

MALIGNANT NEOPLASM LIVER SECONDARY	1977A
METASTASIS LIVER	1977M
BENIGN ADENOMA LIVER	2115AD
BENIGN ANGIOMA LIVER	2115AN
BENIGN CHOLANGIOMA	2115CH
NEUROMA CYSTIC DUCT	2115CN
FIBROMA EXTRAHEPATIC BILE DUCTS	2115EF
HYPERPLASIA FOCAL NODULAR LIVER	2115FH
ADENOMA GALLBLADDER	2115GA
PAPILLOMA GALLBLADDER	2115GP
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ERCP SPHINCTEROTOMY SPHINCTER OF ODDI AND CALCULUS REMOVAL	782B011
ENDOSC SPHINCTEROT SPHINCT ODDI+INSERT BILE DUCT TUBE PROSTH	782B100
OTHER SPECIFIED ENDOSCOPIC INCISION OF SPHINCTER OF ODDI	782By00
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ENDOSCOPIC RETROGRADE RENEWAL TUBAL PROSTHESIS IN BILE DUCT	782D200
ENDOSCOP RETROGRADE REMOVAL TUBAL PROSTHESIS FROM BILE DUCT	782D300
ENDOSCOPIC RETROGRADE PLACEMENT PROSTHESIS IN BILE DUCT OS	782Dy00
ENDOSCOPIC RETROGRADE PLACEMENT PROSTHESIS IN BILE DUCT NOS	782Dz00
OTHER THERAPEUTIC ENDOSCOPIC RETROGRADE BILE DUCT OPERATIONS	782E.00
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ENDOSCOPIC DILATATION OF BILE DUCT NEC	7.82E+102
OTHER THERAPEUTIC ENDOSCOPIC RETROGRADE OP ON BILE DUCT OS	782Ey00
OTHER THERAPEUTIC ENDOSCOPIC RETROGRADE OP ON BILE DUCT NOS	782Ez00
ENDOSC RETROGRADE CHOLANGIOGRAPHY + BIOPSY LESION BILE DUCT	782H000
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THERAPEUTIC PERCUTANEOUS ATTENTION TO BILE DUCT ANASTOMOSIS	782K.11
PERCUTANEOUS DILATION ANAST BILE DUCT+INSERT TUBE PROSTH HFQ	782K000
PERCUTANEOUS DILATION OF ANASTOMOSIS OF BILE DUCT NEC	782K100
THERAPEUTIC PERCUTANEOUS ATTENTION TO BILE DUCT CONNECT OS	782Ky00
THERAPEUTIC PERCUTANEOUS ATTENTION TO BILE DUCT CONNECT NOS	782Kz00
THERAPEUTIC PERCUTANEOUS INSERTION PROSTHESIS INTO BILE DUCT	782L.00
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PERCUTANEOUS INSERT TUBAL PROSTHESIS INTO BOTH HEPATIC DUCTS	782L000
PERCUTAN INSERT TUBAL PROSTHESIS TO RIGHT HEPATIC DUCT NEC	782L100
PERCUTAN INSERT TUBAL PROSTHESIS INTO LEFT HEPATIC DUCT NEC	782L200
PERCUTANEOUS INSERT TUBAL PROSTHESIS INTO HEPATIC DUCT NEC	782L300

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THERAPEUTIC PERCUTANEOUS INSERT PROSTHESIS TO BILE DUCT OS	782Ly00
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REMOVAL PERCUTANEOUSLY INSERTED TUBAL PROSTH FROM BILE DUCT	782M100
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OTHER THERAPEUTIC PERCUTANEOUS OPERATION ON BILE DUCT NOS	782Mz00
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PERCUTAN REMOVAL CALCULUS FROM BILE DUCT ALONG T TUBE TRACK	782N100
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PERCUTANEOUS EXAMINATION OF BILE DUCT NOS	782Pz00
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JAUNDICE	7852
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JAUNDICE INCREASING	7852CR
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JAUNDICE FADING	7852FA
JAUNDICE FLUCTUATING	7852FL
JAUNDICE CHOLESTATIC	7852JC
JAUNDICE PAINLESS	7852PL
EXCISION OR BIOPSY OF PORTA HEPATIS LYMPH NODE	7H62500
[SO]SPHINCTER OF ODDI	7N33400
RUPTURE LIVER	8640R
BILIARY STONE DISSOLVING DIET	8B54.00
CHOLECYSTECTOMY PLANNED	8L1..00
JAUNDICE DRUG INDUCED	9779PN
PORPHYRIA DUE MEDICINAL DRUG	9779PR
RADIATION HEPATITIS	9904HP
REJECTION LIVER TRANSPLANT	9977LT
SYNDROME CYSTIC DUCT	9989CD
SERUM HEPATITIS	9992H
SERUM JAUNDICE	9992J
JAUNDICE AFTER INJECTION/INOCULATION/TRA	9992JA

AMOEBIC LIVER ABSCESS	A053.00
TUBERCULOSIS OF LIVER	A17y400
ACTINOMYCOSIS OF LIVER	A392200
VIRAL HEPATITIS	A70..00
VIRAL HEPATITIS A WITH COMA	A700.00
VIRAL (INFECTIOUS) HEPATITIS A	A701.00
INFECTIVE HEPATITIS	A701.11
VIRAL HEPATITIS B WITH COMA	A702.00
VIRAL (SERUM) HEPATITIS B	A703.00
OTHER SPECIFIED VIRAL HEPATITIS WITH COMA	A704.00
VIRAL HEPATITIS C WITH COMA	A704000
OTHER SPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA NOS	A704z00
OTHER SPECIFIED VIRAL HEPATITIS WITHOUT COMA	A705.00
VIRAL HEPATITIS C WITHOUT MENTION OF HEPATIC COMA	A705000
ACUTE DELTA-(SUPER)INFECTION OF HEPATITIS B CARRIER	A705100
ACUTE HEPATITIS E	A705200
HEPATITIS NON A NON B	A705400
OTHER SPECIFIED VIRAL HEPATITIS WITHOUT MENTION OF COMA NOS	A705z00
UNSPECIFIED VIRAL HEPATITIS WITH COMA	A706.00
CHRONIC VIRAL HEPATITIS	A707.00
CHRONIC VIRAL HEPATITIS B WITH DELTA-AGENT	A707000
CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	A707100
CHRONIC VIRAL HEPATITIS C	A707200
CHRONIC VIRAL HEPATITIS, UNSPECIFIED	A707X00
UNSPECIFIED VIRAL HEPATITIS	A70z.00
HEPATITIS C	A70z000
MUMPS HEPATITIS	A72x000
CYTOMEGALOVIRAL HEPATITIS	A785200
CONGENITAL SYPHILITIC HEPATOMEGALY	A900.15
SECONDARY SYPHILITIC HEPATITIS	A916100
SYPHILIS OF LIVER	A953.00
GONOCOCCAL HEPATITIS	A98yy11
GONOCOCCAL PERIHEPATITIS	A98yy13
LEPTOSPIROSIS ICTEROHAEMORRHAGICA	AA00.00
SPIROCHAETAL JAUNDICE	AA00.11
COCCIDIOMYCOSIS LIVER	AB31.11
HISTOPLASMOSIS LIVER	AB4z600
BLASTOMYCOSIS LIVER	AB50300
CRYPTOCOCCOSIS LIVER	AB65300
CAT LIVER FLUKE INFECTION	AC10.11
CHINESE LIVER FLUKE DISEASE	AC11.11
LIVER FLUKES NOS	AC13.11
SHEEP LIVER FLUKE INFECTION	AC13.12
LIVER ECHINOCOCCUS GRANULOSUS	AC20.00
LIVER ECHINOCOCCUS MULTILOCULARIS	AC25.00
LIVER ECHINOCOCCUS UNSPECIFIED	AC2y.00

CAPILLARIA HEPATICA	AC8y100
TOXOPLASMA HEPATITIS	AD05.00
SARCOIDOSIS	AD5..00
SARCOIDOSIS OF LUNG	AD50.00
SARCOIDOSIS OF LYMPH NODES	AD51.00
SARCOIDOSIS OF LUNG WITH SARCOIDOSIS OF LYMPH NODES	AD52.00
SARCOIDOSIS OF SKIN	AD53.00
SARCOIDOSIS OF INFERIOR TURBINATES	AD54.00
SARCOID ARTHROPATHY	AD55.00
SEQUELAE OF VIRAL HEPATITIS	AE23.00
[X]VIRAL HEPATITIS	AyuB.00
[X]OTHER SPECIFIED ACUTE VIRAL HEPATITIS	AyuB000
[X]OTHER CHRONIC VIRAL HEPATITIS	AyuB100
[X]CHRONIC VIRAL HEPATITIS, UNSPECIFIED	AyuB200
[X]UNSPECIFIED VIRAL HEPATITIS WITH COMA	AyuB300
[X]UNSPECIFIED VIRAL HEPATITIS WITHOUT COMA	AyuB400
[X]ECHINOCOCCOSIS, UNSPECIFIED, OF LIVER	AyuG400
[X]SEQUELAE OF VIRAL HEPATITIS	AyuJ900
MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCTS	B15..00
PRIMARY MALIGNANT NEOPLASM OF LIVER	B150.00
PRIMARY CARCINOMA OF LIVER	B150000
HEPATOBLASTOMA OF LIVER	B150100
PRIMARY ANGIOSARCOMA OF LIVER	B150200
HEPATOCELLULAR CARCINOMA	B150300
PRIMARY MALIGNANT NEOPLASM OF LIVER NOS	B150z00
MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS	B151.00
MALIGNANT NEOPLASM OF INTERLOBULAR BILE DUCTS	B151000
MALIGNANT NEOPLASM OF INTERLOBULAR BILIARY CANALS	B151100
MALIGNANT NEOPLASM OF INTRAHEPATIC BILIARY PASSAGES	B151200
MALIGNANT NEOPLASM OF INTRAHEPATIC CANALICULI	B151300
MALIGNANT NEOPLASM OF INTRAHEPATIC GALL DUCT	B151400
MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS NOS	B151z00
MALIGNANT NEOPLASM OF LIVER UNSPECIFIED	B152.00
SECONDARY MALIGNANT NEOPLASM OF LIVER	B153.00
MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCTS NOS	B15z.00
MALIGNANT NEOPLASM GALLBLADDER AND EXTRAHEPATIC BILE DUCTS	B16..00
MALIGNANT NEOPLASM OF GALLBLADDER	B160.00
CARCINOMA GALLBLADDER	B160.11
MALIGNANT NEOPLASM OF EXTRAHEPATIC BILE DUCTS	B161.00
MALIGNANT NEOPLASM OF CYSTIC DUCT	B161000
MALIGNANT NEOPLASM OF HEPATIC DUCT	B161100
MALIGNANT NEOPLASM OF COMMON BILE DUCT	B161200
CARCINOMA COMMON BILE DUCT	B161211
MALIGNANT NEOPLASM OF SPHINCTER OF ODDI	B161300
MALIGNANT NEOPLASM OF EXTRAHEPATIC BILE DUCTS NOS	B161z00
MALIGNANT NEOPLASM OF AMPULLA OF VATER	B162.00

MALIGNANT NEOPLASM, OVERLAPPING LESION OF BILIARY TRACT	B163.00
MALIGNANT NEOPLASM OTHER GALLBLADDER/EXTRAHEPATIC BILE DUCT	B16y.00
MALIGNANT NEOPLASM GALLBLADDER/EXTRAHEPATIC BILE DUCTS NOS	B16z.00
SECONDARY MALIGNANT NEOPLASM OF LIVER	B577.00
LIVER METASTASES	B577.11
BENIGN NEOPLASM OF LIVER AND BILIARY DUCTS	B715.00
BENIGN NEOPLASM OF BILIARY SYSTEM	B715.11
BENIGN NEOPLASM OF LIVER	B715000
BENIGN NEOPLASM OF INTRAHEPATIC BILE DUCTS	B715100
BENIGN NEOPLASM OF GALLBLADDER	B715200
BENIGN NEOPLASM OF CYSTIC DUCT	B715300
BENIGN NEOPLASM OF HEPATIC DUCT	B715400
BENIGN NEOPLASM OF BILE DUCT	B715500
BENIGN NEOPLASM OF SPHINCTER OF ODDI	B715600
BENIGN NEOPLASM OF AMPULLA OF VATER	B715700
BENIGN NEOPLASM OF LIVER AND BILIARY DUCTS NOS	B715z00
CARCINOMA IN SITU OF LIVER AND BILIARY SYSTEM	B808.00
CARCINOMA IN SITU OF BILIARY SYSTEM	B808.11
CARCINOMA IN SITU OF LIVER	B808000
CARCINOMA IN SITU OF INTRAHEPATIC BILE DUCTS	B808100
CARCINOMA IN SITU OF HEPATIC DUCT	B808200
CARCINOMA IN SITU OF GALL BLADDER	B808300
CARCINOMA IN SITU OF CYSTIC DUCT	B808400
CARCINOMA IN SITU OF COMMON BILE DUCT	B808500
CARCINOMA IN SITU OF AMPULLA OF VATER	B808600
CARCINOMA IN SITU OF SPHINCTER OF ODDI	B808700
CARCINOMA IN SITU OF LIVER OR BILIARY SYSTEM NOS	B808z00
NEOPLASM OF UNCERTAIN BEHAVIOUR OF LIVER AND BILIARY PASSAGE	B903.00
NEOPLASM OF UNCERTAIN BEHAVIOUR OF BILIARY SYSTEM	B903.11
NEOPLASM OF UNCERTAIN BEHAVIOUR OF LIVER	B903000
NEOPLASM OF UNCERTAIN BEHAVIOUR OF INTRA-HEPATIC BILE DUCTS	B903100
NEOPLASM OF UNCERTAIN BEHAVIOUR OF HEPATIC DUCT	B903200
NEOPLASM OF UNCERTAIN BEHAVIOUR OF GALL BLADDER	B903300
NEOPLASM OF UNCERTAIN BEHAVIOUR OF CYSTIC DUCT	B903400
NEOPLASM OF UNCERTAIN BEHAVIOUR OF COMMON BILE DUCT	B903500
NEOPLASM OF UNCERTAIN BEHAVIOUR OF AMPULLA OF VATER	B903600
NEOPLASM OF UNCERTAIN BEHAVIOUR OF SPHINCTER OF ODDI	B903700
NEOP OF UNCERTAIN BEHAVIOUR OF LIVER OR BILIARY PASSAGES NOS	B903z00
[M]HEPATOBILIARY TRACT ADENOMAS AND CARCINOMAS	BB5D.00
[M]BILIARY TRACT ADENOMAS AND ADENOCARCINOMAS	BB5D.11
[M]BILE DUCT ADENOMA	BB5D000
[M]CHOLANGIOMA	BB5D011
[M]BILE DUCT CARCINOMA	BB5D111
[M]BILE DUCT CYSTADENOMA	BB5D200
[M]BILE DUCT CYSTADENOCARCINOMA	BB5D300
[M]LIVER CELL ADENOMA	BB5D400

[M]HEPATOCELLULAR ADENOMA	BB5D411
[M]HEPATOMA, BENIGN	BB5D412
[M]HEPATOCELLULAR CARCINOMA NOS	BB5D500
[M]HEPATOMA NOS	BB5D511
[M]HEPATOMA, MALIGNANT	BB5D512
[M]LIVER CELL CARCINOMA	BB5D513
[M]HEPATOCHOLANGIOMA, BENIGN	BB5D600
[M]COMBINED HEPATOCELLULAR CARCINOMA AND CHOLANGIOCARCINOMA	BB5D700
[M]HEPATOCHOLANGIOCARCINOMA	BB5D711
[M]HEPATOCELLULAR CARCINOMA, FIBROLAMELLAR	BB5D800
[M]HEPATOBILIARY ADENOMA OR CARCINOMA NOS	BB5Dz00
[M]HEPATOBLASTOMA	BBL8.00
[M]EMBRYONAL HEPATOMA	BBL8.11
[X]OTHER SARCOMAS OF THE LIVER	Byu1000
[X]OTHER SPECIFIED CARCINOMAS OF LIVER	Byu1100
CYSTINE STORAGE DISEASE	C300311
GLYCOGENOSIS - GLYCOGEN STORAGE DISEASE	C310.00
GLYCOGEN STORAGE DISEASE	C310.13
GLYCOGENOSIS, TYPE 5	C310012
GENERALISED GLYCOGENOSIS	C310100
GLYCOGENOSIS, TYPE 2	C310113
HEPATORENAL GLYCOGENOSIS	C310200
GLYCOGENOSIS, TYPE 1	C310213
GLYCOGENOSIS OF LIVER AND MUSCLE	C310300
GLYCOGENOSIS OF LIVER AND MUSCLE	C310311
GLYCOGENOSIS, TYPE 3	C310313
GLYCOGENOSIS WITH HEPATIC CIRRHOSIS	C310400
GLYCOGENOSIS, TYPE 4	C310411
OTHER SPECIFIED GLYCOGENOSIS	C310y00
GLYCOGENOSIS NOS	C310z00
ANDERSON'S DISEASE	C327.11
FABRY'S DISEASE	C327.12
GAUCHER'S DISEASE	C327100
FABRY'S DISEASE	C327411
ANDERSON'S DISEASE	C327412
ANDERSON-FABRY DISEASE	C327413
STEATOSIS	C32y500
HEPATIC FAMILIAL STEATOSIS	C32y511
HAEMOCHROMATOSIS	C350000
BRONZED DIABETES	C350011
PIGMENTARY CIRRHOSIS OF LIVER	C350012
HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)	C351000
WILSON'S DISEASE	C351011
HYPERCUPRAEMIA	C351100
DISORDERS OF PORPHYRIN METABOLISM	C371.00
CONGENITAL PORPHYRIA	C371000

ERYTHROPOIETIC PROTOPORPHYRIA	C371100
ACUTE INTERMITTENT PORPHYRIA	C371200
PROTOCOPROPORPHYRIA	C371300
PORPHYRIA CUTANEA TARDA	C371400
COPROPORPHYRIA	C371500
PORPHYRIA NOS	C371z00
AMYLOIDOSIS	C373.00
SPORADIC PRIMARY AMYLOIDOSIS	C373000
FAMILIAL NEUROPATHIC AMYLOID	C373200
FAMILIAL CARDIAC AMYLOID	C373300
SECONDARY AMYLOIDOSIS	C373500
NEPHROPATHIC AMYLOIDOSIS	C373600
PRIMARY AMYLOIDOSIS NEC	C373700
ORGAN LIMITED NON-HEREDITARY AMYLOIDOSIS	C373900
HEREDOFAMILIAL AMYLOIDOSIS, UNSPECIFIED	C373X00
OTHER SPECIFIED AMYLOIDOSIS	C373y00
AMYLOIDOSIS NOS	C373z00
CRIGLER - NAJJAR SYNDROME	C374000
DUBIN - JOHNSON SYNDROME	C374100
ROTOR SYNDROME	C374300
ALPHA-1-ANTITRYPSIN HEPATITIS	C376100
ALPHA-1-ANTITRYPSIN DEFICIENCY	C376200
[X]SARCOIDOSIS OF OTHER AND COMBINED SITES	Cyu0600
[X]OTHER LIPID STORAGE DISORDERS	Cyu8900
[X]OTHER PORPHYRIA	Cyu8H00
[X]OTHER AMYLOIDOSIS	Cyu8L00
[X]HEREDOFAMILIAL AMYLOIDOSIS, UNSPECIFIED	Cyu8U00
FOLATE-DEFICIENCY ANAEMIA DUE TO LIVER DISORDERS	D012400
ACHOLURIC FAMILIAL JAUNDICE	D100.11
DEFICIENCY OF COAGULATION FACTOR DUE TO LIVER DISEASE	D307000
MENINGITIS DUE TO SARCOIDOSIS	F013.00
AUTONOMIC NEUROPATHY DUE TO AMYLOID	F171000
MULTIPLE CRANIAL NERVE PALSIES IN SARCOIDOSIS	F326300
POLYNEUROPATHY IN AMYLOIDOSIS	F374000
POLYNEUROPATHY IN PORPHYRIA	F374800
POLYNEUROPATHY IN SARCOIDOSIS	F374900
MYOPATHY DUE TO AMYLOID	F396000
MYOPATHY DUE TO SARCOIDOSIS	F396500
DIFFUSE CHOLESTEATOSIS	F553400
AMYLOID HEART DISEASE	G557000
SARCOID HEART DISEASE	G558300
SARCOID MYOCARDITIS	G5y7.00
CEREBRAL AMYLOID ANGIOPATHY	G674000
ANEURYSM OF HEPATIC ARTERY	G72yA00
EMBOLISM AND THROMBOSIS OF THE HEPATIC ARTERY	G74y900
PORTAL VEIN THROMBOSIS	G81..00

BUDD - CHIARI SYNDROME (HEPATIC VEIN THROMBOSIS)	G820.00
HEPATIC VEIN THROMBOSIS	G820.11
OESOPHAGEAL VARICES	G85..11
OESOPHAGEAL VARICES WITH BLEEDING	G850.00
OESOPHAGEAL VARICES WITHOUT BLEEDING	G851.00
OESOPHAGEAL VARICES IN DISEASES EC	G852.00
OESOPHAGEAL VARICES WITH BLEEDING IN DISEASES EC	G852000
OESOPHAGEAL VARICES WITHOUT BLEEDING IN DISEASES EC	G852100
OESOPHAGEAL VARICES IN CIRRHOSIS OF THE LIVER	G852200
OESOPHAGEAL VARICES IN ALCOHOLIC CIRRHOSIS OF THE LIVER	G852300
OESOPHAGEAL VARICES IN DISEASES EC NOS	G852z00
GASTRIC VARICES	G857.00
OESOPHAGEAL VARICES NOS	G858.00
[X]OESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE	Gyu9400
EMPYEMA WITH HEPATOPLEURAL FISTULA	H500200
PULMONARY AMYLOIDOSIS	H57y000
PULMONARY SARCOIDOSIS	H57y200
GALLSTONE ILEUS	J503000
SUBHEPATIC ABSCESS	J552000
PERITONITIS DUE TO BILE	J55y300
ACUTE AND SUBACUTE LIVER NECROSIS	J60..00
ACUTE NECROSIS OF LIVER	J600.00
ACUTE HEPATIC FAILURE	J600000
ACUTE LIVER FAILURE	J600011
ACUTE HEPATITIS - NONINFECTIVE	J600100
ACUTE YELLOW ATROPHY	J600200
ACUTE NECROSIS OF LIVER NOS	J600z00
SUBACUTE NECROSIS OF LIVER	J601.00
SUBACUTE HEPATIC FAILURE	J601000
SUBACUTE HEPATITIS - NONINFECTIVE	J601100
SUBACUTE YELLOW ATROPHY	J601200
SUBACUTE NECROSIS OF LIVER NOS	J601z00
ACUTE AND SUBACUTE LIVER NECROSIS NOS	J60z.00
CIRRHOSIS AND CHRONIC LIVER DISEASE	J61..00
ALCOHOLIC FATTY LIVER	J610.00
ACUTE ALCOHOLIC HEPATITIS	J611.00
ALCOHOLIC CIRRHOSIS OF LIVER	J612.00
FLORID CIRRHOSIS	J612.11
LAENNEC'S CIRRHOSIS	J612.12
ALCOHOLIC FIBROSIS AND SCLEROSIS OF LIVER	J612000
ALCOHOLIC LIVER DAMAGE UNSPECIFIED	J613.00
ALCOHOLIC HEPATIC FAILURE	J613000
CHRONIC HEPATITIS	J614.00
CHRONIC PERSISTENT HEPATITIS	J614000
CHRONIC ACTIVE HEPATITIS	J614100
AUTOIMMUNE CHRONIC ACTIVE HEPATITIS	J614111

CHRONIC AGGRESSIVE HEPATITIS	J614200
RECURRENT HEPATITIS	J614300
CHRONIC LOBULAR HEPATITIS	J614400
CHRONIC HEPATITIS UNSPECIFIED	J614y00
CHRONIC HEPATITIS NOS	J614z00
CIRRHOSIS - NON ALCOHOLIC	J615.00
PORTAL CIRRHOSIS	J615.11
UNILOBULAR PORTAL CIRRHOSIS	J615000
MULTILOBULAR PORTAL CIRRHOSIS	J615100
POSTNECROTIC CIRRHOSIS OF LIVER	J615111
MIXED PORTAL CIRRHOSIS	J615200
DIFFUSE NODULAR CIRRHOSIS	J615300
FATTY PORTAL CIRRHOSIS	J615400
HYPERTROPHIC PORTAL CIRRHOSIS	J615500
CAPSULAR PORTAL CIRRHOSIS	J615600
CARDIAC PORTAL CIRRHOSIS	J615700
CONGESTIVE CIRRHOSIS	J615711
JUVENILE PORTAL CIRRHOSIS	J615800
CHILDHOOD FUNCTION CIRRHOSIS	J615811
INDIAN CHILDHOOD CIRRHOSIS	J615812
PIGMENTARY PORTAL CIRRHOSIS	J615900
PIPE-STEM PORTAL CIRRHOSIS	J615A00
TOXIC PORTAL CIRRHOSIS	J615B00
XANTHOMATOUS PORTAL CIRRHOSIS	J615C00
BACTERIAL PORTAL CIRRHOSIS	J615D00
CARDITUBERCULOUS CIRRHOSIS	J615E00
SYPHILITIC PORTAL CIRRHOSIS	J615F00
ZOOPARASITIC PORTAL CIRRHOSIS	J615G00
INFECTIOUS CIRRHOSIS NOS	J615H00
PORTAL CIRRHOSIS UNSPECIFIED	J615y00
NON-ALCOHOLIC CIRRHOSIS NOS	J615z00
MACRONODULAR CIRRHOSIS OF LIVER	J615z11
CRYPTOGENIC CIRRHOSIS OF LIVER	J615z12
CIRRHOSIS OF LIVER NOS	J615z13
LAENNEC'S CIRRHOSIS, NON-ALCOHOLIC	J615z14
HEPATIC FIBROSIS	J615z15
BILIARY CIRRHOSIS	J616.00
PRIMARY BILIARY CIRRHOSIS	J616000
SECONDARY BILIARY CIRRHOSIS	J616100
BILIARY CIRRHOSIS OF CHILDREN	J616200
BILIARY CIRRHOSIS NOS	J616z00
ALCOHOLIC HEPATITIS	J617.00
CHRONIC ALCOHOLIC HEPATITIS	J617000
OTHER NON-ALCOHOLIC CHRONIC LIVER DISEASE	J61y.00
CHRONIC YELLOW LIVER ATROPHY	J61y000
NON-ALCOHOLIC FATTY LIVER	J61y100

HEPATOSPLENOMEGALY	J61y200
PORTAL FIBROSIS WITHOUT CIRRHOSIS	J61y300
HEPATIC FIBROSIS	J61y400
HEPATIC SCLEROSIS	J61y500
HEPATIC FIBROSIS WITH HEPATIC SCLEROSIS	J61y600
STEATOSIS OF LIVER	J61y700
OTHER NON-ALCOHOLIC CHRONIC LIVER DISEASE NOS	J61yz00
CHRONIC LIVER DISEASE NOS	J61z.00
LIVER ABSCESS AND SEQUELAE OF CHRONIC LIVER DISEASE	J62..00
LIVER ABSCESS - EXCLUDING AMOEBIC LIVER ABSCESS	J620.00
LIVER ABSCESS DUE TO PORTAL PYAEMIA	J620000
LIVER ABSCESS DUE TO CHOLANGITIS	J620100
LIVER ABSCESS VIA HEPATIC ARTERY	J620200
LIVER ABSCESS VIA UMBILICUS	J620300
LIVER ABSCESS DUE TO DIRECT EXTENSION	J620400
LIVER ABSCESS NOS	J620z00
PORTAL PYAEMIA	J621.00
PHLEBITIS OF PORTAL VEIN	J621.11
HEPATIC COMA	J622.00
ENCEPHALOPATHY - HEPATIC	J622.11
PORTAL HYPERTENSION	J623.00
HEPATORENAL SYNDROME	J624.00
[X] HEPATIC FAILURE	J625.00
[X] LIVER FAILURE	J625.11
OTHER SEQUELAE OF CHRONIC LIVER DISEASE	J62y.00
HEPATIC FAILURE NOS	J62y.11
LIVER FAILURE NOS	J62y.12
HEPATIC FAILURE	J62y.13
LIVER ABSCESS AND CHRONIC LIVER DISEASE CAUSING SEQUELAE NOS	J62z.00
OTHER LIVER DISORDERS	J63..00
CHRONIC PASSIVE LIVER CONGESTION	J630.00
HEPATITIS IN VIRAL DISEASES EC	J631.00
HEPATITIS IN COXSACKIE VIRUS	J631000
HEPATITIS IN CYTOMEGALIC INCLUSION VIRUS	J631100
HEPATITIS IN INFECTIOUS MONONUCLEOSIS	J631200
HEPATITIS IN MUMPS	J631300
HEPATITIS IN YELLOW FEVER	J631400
HEPATITIS IN OTHER VIRAL DISEASE	J631500
HEPATITIS + ADENOVIRUS	J631600
HEPATITIS IN VIRAL DISEASES EC NOS	J631z00
HEPATITIS IN OTHER INFECTIOUS DISEASES EC	J632.00
HEPATITIS IN MALARIA	J632000
HEPATITIS IN LATE SYPHILIS	J632100
HEPATITIS IN SECONDARY SYPHILIS	J632200
HEPATITIS IN TOXOPLASMOSIS	J632300
HEPATITIS IN INFECTIOUS DISEASES EC NOS	J632z00

HEPATITIS UNSPECIFIED	J633.00
TOXIC HEPATITIS	J633000
HEPATITIS UNSPECIFIED NOS	J633z00
HEPATIC INFARCTION	J634.00
TOXIC LIVER DISEASE	J635.00
TOXIC LIVER DISEASE WITH CHOLESTASIS	J635000
TOXIC LIVER DISEASE WITH HEPATIC NECROSIS	J635100
TOXIC LIVER DISEASE WITH ACUTE HEPATITIS	J635200
TOXIC LIVER DISEASE WITH CHRONIC PERSISTENT HEPATITIS	J635300
TOXIC LIVER DISEASE WITH CHRONIC LOBULAR HEPATITIS	J635400
TOXIC LIVER DISEASE WITH CHRONIC ACTIVE HEPATITIS	J635500
TOXIC LIVER DISEASE WITH FIBROSIS AND CIRRHOSIS OF LIVER	J635600
TOXIC LIVER DISEASE, UNSPECIFIED	J635X00
CENTRAL HAEMORRHAGIC NECROSIS OF LIVER	J636.00
HEPATIC VENO-OCCLUSIVE DISEASE	J637.00
PELIOSIS HEPATIS	J638.00
HEPATIC GRANULOMAS IN BERYLLIOSIS	J639.00
HEPATIC GRANULOMAS IN SARCOIDOSIS	J63A.00
GRANULOMATOUS HEPATITIS, NOT ELSEWHERE CLASSIFIED	J63X.00
OTHER SPECIFIED LIVER DISORDER	J63y.00
HEPATOPTOSIS	J63y000
NONSPECIFIC REACTIVE HEPATITIS	J63y100
LIVER CYST	J63y200
OTHER SPECIFIED LIVER DISORDER NOS	J63yz00
LIVER DISORDER NOS	J63z.00
CHOLELITHIASIS	J64..00
BILE DUCT CALCULUS	J64..11
CALCULUS - BILIARY	J64..12
CYSTIC DUCT CALCULUS	J64..13
GALLBLADDER CALCULUS	J64..14
GALLSTONES	J64..15
STONE - BILIARY	J64..16
GALLBLADDER CALCULUS WITH ACUTE CHOLECYSTITIS	J640.00
GALLBLADDER CALCULUS WITH ACUTE CHOLECYSTITIS +NO OBSTRUCT	J640000
GALLBLADDER CALCULUS WITH ACUTE CHOLECYSTITIS + OBSTRUCTION	J640100
GALLBLADDER CALCULUS WITH ACUTE CHOLECYSTITIS - OBST NOS	J640z00
GALLBLADDER CALCULUS WITH OTHER CHOLECYSTITIS	J641.00
GALLBLADDER CALCULUS WITH OTHER CHOLECYSTITIS +NO OBSTRUCT	J641000
GALLBLADDER CALCULUS WITH OTHER CHOLECYSTITIS + OBSTRUCT	J641100
GALLBLADDER CALCULUS WITH OTHER CHOLECYSTITIS - OBSTRUCT NOS	J641z00
GALLBLADDER CALCULUS WITHOUT MENTION OF CHOLECYSTITIS	J642.00
GALLBLADDER CALCULUS WITHOUT MENTION OF CHOLECYSTITIS	J642.11
GALLBLADDER CALCULUS WITHOUT MENTION CHOLECYSTITIS +NO OBSTR	J642000
GALLBLADDER CALCULUS WITHOUT MENTION CHOLECYSTITIS + OBSTRUC	J642100
BILIARY COLIC	J642200
GALLBLADDER CALCULUS WITHOUT CHOLECYSTITIS AND OBSTRUCT NOS	J642z00

BILE DUCT CALCULUS WITH ACUTE CHOLECYSTITIS	J643.00
BILE DUCT CALCULUS + ACUTE CHOLECYSTITIS AND NO OBSTRUCTION	J643000
BILE DUCT CALCULUS + ACUTE CHOLECYSTITIS AND OBSTRUCTION	J643100
BILE DUCT CALCULUS + ACUTE CHOLECYSTITIS - OBSTRUCT NOS	J643z00
BILE DUCT CALCULUS WITH OTHER CHOLECYSTITIS	J644.00
BILE DUCT CALCULUS + OTHER CHOLECYSTITIS AND NO OBSTRUCTION	J644000
BILE DUCT CALCULUS + OTHER CHOLECYSTITIS AND OBSTRUCTION	J644100
BILE DUCT CALCULUS + OTHER CHOLECYSTITIS - OBSTRUCTION NOS	J644z00
BILE DUCT CALCULUS WITHOUT MENTION OF CHOLECYSTITIS	J645.00
CHOLEDOCHOLITHIASIS	J645.11
BILE DUCT CALCULUS WITHOUT CHOLECYSTITIS, NO OBSTRUCTION	J645000
BILE DUCT CALCULUS WITHOUT CHOLECYSTITIS WITH OBSTRUCTION	J645100
BILE DUCT CALCULUS NOS	J645200
BILE DUCT CALCULUS WITHOUT CHOLECYSTITIS NOS	J645z00
CALCULUS OF BILE DUCT WITH CHOLANGITIS	J646.00
CHOLELITHIASIS NOS	J64z.00
CHOLELITHIASIS WITHOUT OBSTRUCTION NOS	J64z000
CHOLELITHIASIS WITH OBSTRUCTION NOS	J64z100
CHOLELITHIASIS NOS	J64zz00
OTHER GALLBLADDER DISORDERS	J65..00
ACUTE CHOLECYSTITIS	J650.00
ABSCESS OF GALLBLADDER	J650.11
EMPYEMA OF GALLBLADDER	J650.12
ACUTE CHOLECYSTITIS UNSPECIFIED	J650000
ACUTE ANGIOCHOLECYSTITIS	J650100
ACUTE EMPHYSEMATOUS CHOLECYSTITIS	J650200
ACUTE SUPPURATIVE CHOLECYSTITIS	J650300
ACUTE GANGRENOUS CHOLECYSTITIS	J650400
ACUTE CHOLECYSTITIS NOS	J650z00
OTHER CHOLECYSTITIS	J651.00
CHRONIC CHOLECYSTITIS	J651000
OTHER CHOLECYSTITIS OS	J651y00
CHOLECYSTITIS NOS	J651z00
OBSTRUCTION OF GALLBLADDER	J652.00
OCCLUSION OF GALLBLADDER	J652000
STENOSIS OF GALLBLADDER	J652100
OCCLUSION OF CYSTIC DUCT	J652200
STENOSIS OF CYSTIC DUCT	J652300
OBSTRUCTION OF GALLBLADDER NOS	J652z00
MUCOCELE OF GALLBLADDER	J653.00
HYDROPS OF GALLBLADDER	J653.11
PERFORATION OF GALLBLADDER	J654.00
RUPTURE OF GALLBLADDER	J654000
RUPTURE OF CYSTIC DUCT	J654100
PERFORATION OF GALLBLADDER NOS	J654z00
FISTULA OF GALLBLADDER	J655.00

BILIARY FISTULA	J655000
CHOLECYSTOGASTRIC FISTULA	J655100
CHOLECYSTODUODENAL FISTULA	J655200
CHOLECYSTOENTERIC FISTULA	J655300
FISTULA OF GALLBLADDER NOS	J655z00
CHOLESTEROLOSIS OF GALLBLADDER	J656.00
STRAWBERRY GALLBLADDER	J656.11
OTHER SPECIFIED GALLBLADDER DISORDERS	J65y.00
ADHESIONS OF GALLBLADDER	J65y000
ADHESIONS OF CYSTIC DUCT	J65y100
ATROPHY OF GALLBLADDER	J65y200
ATROPHY OF CYSTIC DUCT	J65y300
CYST OF GALLBLADDER	J65y400
CYST OF CYSTIC DUCT	J65y500
HYPERTROPHY OF GALLBLADDER	J65y600
HYPERTROPHY OF CYSTIC DUCT	J65y700
ULCER OF GALLBLADDER	J65y800
ULCER OF CYSTIC DUCT	J65y900
NONFUNCTIONING GALLBLADDER	J65yA00
BILIARY DYSKINESIA	J65yB00
POLYP OF GALLBLADDER	J65yC00
OTHER SPECIFIED GALLBLADDER DISORDER NOS	J65yz00
OTHER GALLBLADDER DISORDERS NOS	J65z.00
OTHER BILIARY TRACT DISORDERS	J66..00
POSTCHOLECYSTECTOMY SYNDROME	J660.00
CHOLANGITIS	J661.00
ACUTE CHOLANGITIS	J661000
CHRONIC CHOLANGITIS	J661100
RECURRENT CHOLANGITIS	J661200
SUPPURATIVE CHOLANGITIS	J661300
ASCENDING CHOLANGITIS	J661400
CHOLANGITIS LENTA	J661500
OBLITERATIVE CHOLANGITIS	J661600
PRIMARY SCLEROSING CHOLANGITIS	J661700
SECONDARY SCLEROSING CHOLANGITIS	J661800
SCLEROSING CHOLANGITIS UNSPECIFIED	J661900
OTHER CHOLANGITIS	J661y00
CHOLANGITIS NOS	J661z00
OBSTRUCTION OF BILE DUCT	J662.00
OCCLUSION OF BILE DUCT	J662000
STRICTURE OF BILE DUCT	J662100
OBSTRUCTION OF BILE DUCT NOS	J662z00
PERFORATION OF BILE DUCT	J663.00
FISTULA OF BILE DUCT	J664.00
FISTULA OF BILE DUCT NOS	J664z00
SPASM OF SPHINCTER OF ODDI	J665.00

OTHER BILE DUCT DISORDERS	J66y.00
ADHESIONS OF BILE DUCT	J66y000
ATROPHY OF BILE DUCT	J66y100
CYST OF BILE DUCT	J66y200
HYPERTROPHY OF BILE DUCT	J66y300
STASIS OF BILE DUCT	J66y400
ULCER OF BILE DUCT	J66y500
OBSTRUCTIVE JAUNDICE NOS	J66y600
POST CHOLECYSTECTOMY BILE LEAKAGE	J66y700
OTHER BILE DUCT DISORDER NOS	J66yz00
BILE DUCT DISORDER NOS	J66z.00
[X]DISEASES OF THE LIVER	Jyu7.00
[X]TOXIC LIVER DISEASE WITH OTHER DISORDERS OF LIVER	Jyu7000
[X]OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER	Jyu7100
[X]OTHER SPECIFIED INFLAMMATORY LIVER DISEASES	Jyu7200
[X]OTHER SPECIFIED DISEASES OF LIVER	Jyu7300
[X]LIVER DISORDERS IN INFECTIOUS AND PARASITIC DISEASES CE	Jyu7400
[X]LIVER DISORDERS IN OTHER DISEASES CLASSIFIED ELSEWHERE	Jyu7500
[X]TOXIC LIVER DISEASE, UNSPECIFIED	Jyu7600
[X]GRANULOMATOUS HEPATITIS, NOT ELSEWHERE CLASSIFIED	Jyu7700
[X]DISORDERS OF THE GALLBLADDER, BILIARY TRACT AND PANCREAS	Jyu8.00
[X]OTHER CHOLELITHIASIS	Jyu8000
[X]OTHER CHOLECYSTITIS	Jyu8100
[X]OTHER SPECIFIED DISEASES OF GALLBLADDER	Jyu8200
[X]OTHER SPECIFIED DISEASES OF BILIARY TRACT	Jyu8300
[X]DISORDERS OF GALLBLADDER+BILIARY TRACT IN DISEASES CE	Jyu8600
NEPHROTIC SYNDROME IN AMYLOIDOSIS	K01x000
FUND HOLDING OP OESOPHAGEAL VARICES	K298 FH
LIGATION OESOPHAGEAL VARICES	K2981
INJECTION OESOPHAGEAL VARICES	K2982
HEPATECTOMY	K500
EXCISION HEPATIC ABSCESS	K5001
REMOVAL HYDATID CYST	K5001C
TRANSPLANTATION LIVER	K5005
HEPATORRHAPHY	K502
LIVER OPERATION	K509
HEPATOSTOMY	K5091
HEPATOTOMY	K5092
EXPLORATION BILE DUCT	K510 AA
CRUSHING CALCULUS BILIARY	K511
LITHOTOMY HEPATIC DUCT	K511 AA
LITHOTOMY BILE DUCT	K511 AB
REMOVAL CALCULUS BILE DUCT	K511 AC
DRAINAGE BILE DUCT	K512
ROUX- Y ANASTOMOSIS BILE DUCT TO BOWEL	K513 AA
OPERATION ON THE BILE DUCTS	K519

FUND HOLDING OP BILE DUCT	K519 FH
INSERTION TUBE HEPATIC DUCT	K519 H
REMOVAL STONES GALLBLADDER	K521 AB
CHOLECYSTECTOMY	K522
CHOLECYSTECTOMY PLANNED	K522 X
CHOLECYSTENTEROSTOMY	K524 B
GASTROCHOLECYSTOSTOMY	K524 G
CHOLECYSTOSTOMY	K529
ACUTE LIVER NECROSIS FOLLOWING ABORTIVE PREGNANCY	L09y000
HELLP - SYNDROME HAEMOLYSIS, ELEV LIVER ENZYME LOW PLATELETS	L12A.00
LIVER DISORDER IN PREGNANCY	L167.00
LIVER DISORDER IN PREGNANCY UNSPECIFIED	L167000
LIVER DISORDER IN PREGNANCY - DELIVERED	L167100
LIVER DISORDER IN PREGNANCY - NOT DELIVERED	L167200
LIVER DISORDER IN PREGNANCY NOS	L167z00
VIRAL HEPATITIS COMP PREGNANCY, CHILDBIRTH & THE PUERPERIUM	L176500
LIVER FUNCTION TEST ABNORMAL	L3260AB
LIVER BIOCHEMICAL DYSFUNCTION	L3262AB
LIVER ENZYMES ABNORMAL	L3263AB
RAISED LIVER ENZYMES	L3263H
HEPATIC FUNCTION ABNORMAL	L3264AB
PUERPERAL PERITONITIS - DELIVERED WITH POSTNATAL COMP	L402100
ANTIBODIES ANTI-MITOCHONDRIAL PRESENT	L6652DM
ANTIBODIES HEPATITIS B CORE PRESENT	L6652DV
ANTIBODIES HEPATITIS B E PRESENT	L6652DW
ANTIBODIES HEPATITIS E PRESENT	L6652DY
CHLOASMA HEPATICUM	M290400
AMYLOIDOSIS OF SKIN	M2y9.00
ARTHROPATHY IN AMYLOIDOSIS	N030200
MYOSITIS IN SARCOIDOSIS	N233200
[X]MYOSITIS IN SARCOIDOSIS CLASSIFIED ELSEWHERE	Nyu8900
ANOMALOUS PORTAL VEIN TERMINATION	P743.00
PORTAL VEIN - HEPATIC ARTERY FISTULA	P744.00
LIVER AND BILIARY SYSTEM ANOMALIES	PB6..00
BILE DUCT ANOMALIES	PB6..11
BILIARY ANOMALIES	PB6..12
GALLBLADDER ANOMALIES	PB6..13
LIVER ANOMALIES	PB6..14
LIVER AND BILIARY SYSTEM ANOMALIES, UNSPECIFIED	PB60.00
LIVER ANOMALY, UNSPECIFIED	PB60000
GALLBLADDER ANOMALY, UNSPECIFIED	PB60100
BILE DUCT ANOMALY, UNSPECIFIED	PB60200
UNSPECIFIED LIVER AND BILIARY SYSTEM ANOMALY NOS	PB60z00
BILIARY ATRESIA	PB61.00
BILE DUCT ATRESIA	PB61.11
CONGENITAL ABSENCE OF BILE DUCT	PB61000

AGENESIS OF BILE DUCT	PB61011
CONGENITAL HYPOPLASIA OF BILE DUCT	PB61100
CONGENITAL OBSTRUCTION OF BILE DUCT	PB61200
CONGENITAL STRICTURE OF BILE DUCT	PB61300
CONGENITAL STRICTURE OF COMMON BILE DUCT	PB61311
ATRESIA OF BILE DUCT	PB61400
INTRAHEPATIC ATRESIA OF BILE DUCT	PB61411
EXTRAHEPATIC ATRESIA OF BILE DUCT	PB61412
CONGENITAL ABSENCE OF HEPATIC DUCTS	PB61500
AGENESIS OF HEPATIC DUCTS	PB61511
ATRESIA OF HEPATIC DUCTS	PB61600
BILIARY ATRESIA NOS	PB61z00
CONGENITAL CYSTIC LIVER DISEASE	PB62.00
CONGENITAL HEPATIC CYST	PB62.11
CONGENITAL POLYCYSTIC LIVER DISEASE	PB62000
FIBROCYSTIC LIVER DISEASE	PB62100
CONGENITAL CYSTIC LIVER DISEASE NOS	PB62z00
CONGENITAL ABSENCE OF LIVER AND GALLBLADDER	PB63.00
CONGENITAL ABSENCE OF GALLBLADDER	PB63000
AGENESIS OF GALLBLADDER	PB63011
CONGENITAL ABSENCE OF LIVER LOBE	PB63100
CONGENITAL AGENESIS OF LIVER LOBE	PB63111
CONGENITAL ABSENCE OF LIVER,TOTAL	PB63400
CONGENITAL AGENESIS LIVER,TOTAL	PB63411
ABSENCE OF LIVER OR GALLBLADDER NOS	PB63z00
LIVER AND BILIARY DUPLICATION	PB64.00
DUPLICATION OF BILIARY DUCT	PB64000
DUPLICATION OF CYSTIC DUCT	PB64100
DUPLICATION OF GALLBLADDER	PB64200
DUPLICATION OF LIVER	PB64300
ACCESSORY LIVER	PB64311
ACCESSORY HEPATIC DUCTS	PB64400
LIVER OR BILIARY DUPLICATION NOS	PB64z00
OTHER LIVER AND BILIARY ANOMALIES	PB6y.00
CONGENITAL CHOLEDOCHAL CYST	PB6y000
CONGENITAL HEPATOMEGALY	PB6y100
CONGENITAL FLOATING GALLBLADDER	PB6y200
INTRAHEPATIC GALLBLADDER	PB6y400
HYPOPLASIA OF GALLBLADDER	PB6y500
ATROPHY OF LEFT LOBE OF LIVER	PB6y600
CONGENITAL DILATION OF BILE DUCT	PB6y700
CONGENITAL DIVERTICULUM OF BILE DUCT	PB6y800
LIVER HYPERPLASIA	PB6y900
OTHER CONGENITAL ANOMALY OF LIVER	PB6yw00
LIVER HAMARTOMA	PB6yw11
TRILOBULAR LIVER	PB6yw13

OTHER CONGENITAL ANOMALY OF GALLBLADDER	PB6yx00
OTHER CONGENITAL ANOMALY OF HEPATIC OR BILE DUCTS	PB6yy00
CONGENITAL KINK OF CYSTIC DUCT	PB6yy11
OTHER LIVER OR BILIARY SYSTEM ANOMALIES NOS	PB6yz00
LIVER OR BILIARY SYSTEM ANOMALIES NOS	PB6z.00
[X]OTHER CONGENITAL MALFORMATIONS OF GALLBLADDER	Pyu5C00
[X]OTHER CONGENITAL MALFORMATIONS OF BILE DUCTS	Pyu5D00
[X]OTHER CONGENITAL MALFORMATIONS OF LIVER	Pyu5E00
LIVER SUBCAPSULAR HAEMATOMA DUE TO BIRTH TRAUMA	Q20y100
LIVER RUPTURE DUE TO BIRTH TRAUMA	Q20y400
CONGENITAL VIRAL HEPATITIS	Q409.00
CONGENITAL HEPATITIS A INFECTION	Q409000
CONGENITAL HEPATITIS B INFECTION	Q409100
OTHER SPECIFIED CONGENITAL VIRAL HEPATITIS	Q409y00
CONGENITAL VIRAL HEPATITIS NOS	Q409z00
KERNICTERUS DUE TO ISOIMMUNISATION	Q424.00
OTHER PERINATAL JAUNDICE	Q43..00
PERINATAL JAUNDICE FROM HEREDITARY HAEMOLYTIC ANAEMIAS	Q430.00
NEONATAL JAUNDICE + GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFIC.	Q430000
PERINATAL JAUNDICE FROM HEREDITARY HAEMOLYTIC ANAEMIA NOS	Q430z00
PERINATAL JAUNDICE FROM OTHER EXCESSIVE HAEMOLYSIS	Q431.00
PERINATAL JAUNDICE FROM BRUISING	Q431000
PERINATAL JAUNDICE FROM MATERNAL TRANSMISSION DRUG OR TOXIN	Q431100
PERINATAL JAUNDICE FROM INFECTION	Q431200
PERINATAL JAUNDICE FROM POLYCYTHAEMIA	Q431300
PERINATAL JAUNDICE FROM SWALLOWED MATERNAL BLOOD	Q431400
PERINATAL JAUNDICE FROM BLEEDING	Q431500
PERINATAL JAUNDICE FROM OTHER SPECIFIED HAEMOLYSIS	Q431y00
PERINATAL JAUNDICE FROM HAEMOLYSIS NOS	Q431z00
PRETERM DELIVERY ASSOCIATED JAUNDICE	Q432.00
OTHER NEONATAL JAUNDICE - DELAYED CONJUGATION OTHER CAUSE	Q433.00
DELAYED CONJUGATION CAUSING NEONATAL JAUNDICE, UNSPECIFIED	Q433000
DELAYED CONJUGATION CAUSING NEONATAL JAUNDICE + DISEASE EC	Q433100
BREAST FEEDING INHIBITORS CAUSING NEONATAL JAUNDICE	Q433200
NEONATAL JAUNDICE WITH CRIGLER-NAJJAR SYNDROME	Q433400
NEONATAL JAUNDICE WITH DUBIN-JOHNSON SYNDROME	Q433500
NEONATAL JAUNDICE WITH GILBERT'S SYNDROME	Q433600
NEONATAL JAUNDICE WITH CONGENITAL HYPOTHYROIDISM	Q433700
NEONATAL JAUNDICE WITH PORPHYRIA	Q433800
NEONATAL JAUNDICE WITH ROTOR'S SYNDROME	Q433900
NEONATAL JAUNDICE FROM BREAST MILK INHIBITOR	Q433A00
DELAYED CONJUGATION CAUSING NEONATAL JAUNDICE OS	Q433y00
NEONATAL JAUNDICE - DEFICIENCY ENZYME FOR BILIRUBIN CONJUG.	Q433y11
DELAYED CONJUGATION CAUSING NEONATAL JAUNDICE NOS	Q433z00
PERINATAL JAUNDICE DUE TO HEPATOCELLULAR DAMAGE	Q434.00
PERINATAL HEPATITIS CAUSING JAUNDICE, UNSPECIFIED	Q434000

GIANT CELL HEPATITIS CAUSING NEONATAL JAUNDICE	Q434100
PERINATAL JAUNDICE DUE TO HEPATOCELLULAR DAMAGE NOS	Q434z00
PERINATAL JAUNDICE DUE TO OTHER CAUSE	Q435.00
PERINATAL JAUNDICE DUE TO CONGENITAL OBSTRUCTION BILE DUCT	Q435000
PERINATAL JAUNDICE DUE TO GALACTOSAEMIA	Q435100
PERINATAL JAUNDICE DUE TO MUCOVISCIDOSIS	Q435200
PERINATAL JAUNDICE DUE TO OTHER SPECIFIED CAUSE	Q435z00
FETAL AND NEONATAL JAUNDICE, UNSPECIFIED	Q436.00
ICTERUS NEONATORUM, UNSPECIFIED	Q436000
NEWBORN PHYSIOLOGICAL JAUNDICE NOS	Q436200
UNSPECIFIED FETAL OR NEONATAL JAUNDICE NOS	Q436z00
KERNICTERUS NOT DUE TO ISOIMMUNISATION	Q437.00
KERNICTERUS OF NEWBORN NOS	Q437z00
PERINATAL JAUNDICE NOS	Q43z.00
BRONZE BABY	Q47y100
CONGENITAL HEPATIC FIBROSIS	Q48yz11
[X]OTHER SPECIFIED KERNICTERUS	Qyu5700
[X]NEONATAL JAUNDICE DUE/OTHER SPECIFD EXCESSIVE HAEMOLYSIS	Qyu5900
[X]NEONATAL JAUNDICE FROM OTHER+UNSPCF HEPATOCELLULAR DAMAGE	Qyu5A00
[X]NEONATAL JAUNDICE FROM OTHER SPECIFIED CAUSES	Qyu5B00
[D]JAUNDICE (NOT OF NEWBORN)	R024.00
[D]ICTERUS NOS	R024100
[D]JAUNDICE	R024111
[D]JAUNDICE (NOT OF NEWBORN) NOS	R024z00
[D]LIVER ENLARGEMENT	R091000
[D]BILIARY TRACT X-RAY OR SCAN ABNORMALITY	R133.00
[D]BILIARY X-RAY OR SCAN ABNORMALITY NOS	R133z00
[D]ABNORMAL LIVER FUNCTION TEST	R148.00
[D]ABNORMAL LIVER SCAN	R148000
[D]ABNORMAL LIVER FUNCTION TEST NOS	R148z00
INJURY TO LIVER	S74..00
CLOSED INJURY OF LIVER	S740.00
LIVER INJURY WITHOUT OPEN WOUND INTO CAVITY, UNSPECIFIED	S740000
LIVER HAEMATOMA AND CONTUSION WITHOUT OPEN WOUND INTO CAVITY	S740100
LIVER MINOR LACERATION WITHOUT OPEN WOUND INTO CAVITY	S740200
LIVER MODERATE LACERATION WITHOUT OPEN WOUND INTO CAVITY	S740300
LIVER MAJOR LACERATION WITHOUT OPEN WOUND INTO CAVITY	S740400
OTHER LIVER LACERATION WITHOUT OPEN WOUND INTO CAVITY	S740y00
LIVER INJURIES WITHOUT OPEN WOUND INTO CAVITY, NOS	S740z00
OPEN INJURY OF LIVER	S741.00
LIVER INJURY WITH OPEN WOUND INTO CAVITY, UNSPECIFIED	S741000
LIVER HAEMATOMA AND CONTUSION WITH OPEN WOUND INTO CAVITY	S741100
LIVER MINOR LACERATION WITH OPEN WOUND INTO CAVITY	S741200
LIVER MODERATE LACERATION WITH OPEN WOUND INTO CAVITY	S741300
LIVER MAJOR LACERATION WITH OPEN WOUND INTO CAVITY	S741400
OTHER LIVER INJURY WITH OPEN WOUND INTO CAVITY	S741y00

LIVER INJURY WITH OPEN WOUND INTO CAVITY, NOS	S741z00
INJURY TO LIVER, NOS	S74z.00
RUPTURED LIVER NOS	S74z.11
BILE DUCT/GALLBLADDER INJURY WITHOUT OPEN WOUND INTO CAVITY	S780200
BILE DUCT INJURY WITHOUT OPEN WOUND INTO CAVITY	S780211
GALLBLADDER INJURY WITHOUT OPEN WOUND INTO CAVITY	S780212
BILE DUCT/GALLBLADDER INJURY WITH OPEN WOUND INTO CAVITY	S781200
BILE DUCT INJURY WITH OPEN WOUND INTO CAVITY	S781211
GALLBLADDER INJURY WITH OPEN WOUND INTO CAVITY	S781212
HEPATIC VEIN INJURY	SB21100
HEPATIC ARTERY INJURY	SB22200
PORTAL AND SPLENIC VEIN INJURY	SB23.00
PORTAL VEIN INJURY	SB23200
PORTAL AND SPLENIC VEIN INJURY NOS	SB23z00
MECHANICAL COMPLICATION OF BILE DUCT PROSTHESIS	SP05100
LIVER TRANSPLANT FAILURE AND REJECTION	SP08600
HEPATIC FAILURE AS A COMPLICATION OF CARE	SP14200
LIVER FAILURE AS A COMPLICATION OF CARE	SP14211
HEPATORENAL SYNDROME AS A COMPLICATION OF CARE	SP14300
LIVER TRANSPLANT WITH COMPLICATION, WITHOUT BLAME	TB00200
CONTACT SERUM HEPATITIS	Y409 E
CHOLECYSTOGRAM ABNORMAL	Y500 BA
DIETARY ADVICE FOR HEPATIC DISORDER	ZC2CH00
DIETARY ADVICE FOR LIVER DISEASE	ZC2CH11
[V]VIRAL HEPATITIS CARRIER	ZV02600
[V]HEPATITIS AUSTRALIA ANTIGEN CARRIER	ZV02612
[V]PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LIVER	ZV10015
[V]LIVER TRANSPLANTED	ZV42700
[V]ASSESSMENT FOR LIVER TRANSPLANT	ZV7C000

Appendix III-b Codes for death

Description	medcode
O/E - dead	22J..00
O/E - dead - condition fatal	22J..11
Death	22J..12
Died	22J..13
Patient died	22J..14
O/E - dead - unexpected	22J1.00
O/E - dead - expected	22J2.00
O/E - dead - unattended death	22J3.00
O/E - dead - sudden death	22J4.00
O/E - dead - cot death	22J5.00
O/E - dead - suspicious death	22J6.00
Postneonatal death	22J7.00
O/E - dead NOS	22JZ.00
O/E - respiratory death	236..12
DELIVERY SUDDEN DEATH (MOTHER)	661 DH
SUDDEN DEATH CHILDBIRTH CAUSE UNKNOWN	661 DN
DELIVERY DEATH DUE ANAESTHETIC	662 N
SUDDEN DEATH PUERPERIUM CAUSE UNKNOWN	6770AD
NEONATAL DEATH	7789ND
DEATH IN UTERO	7799A
STILLBIRTH	7799B
SUDDEN DEATH INFANT SYNDROME	795 B
COT DEATH	795 C
DROPPED DEAD	795 DR
SUDDEN DEATH NONVIOLENT	795 N
FOUND DEAD	7962
UNKNOWN CAUSE DEATH	7963
Preoperative anaesthetic death	7L1M000
Died in hospital	8HG..00
Death in hospital	8HG..11
Registration ghost - deceased	9134
Registration ghost - dead	9134.11
Registration ghost - died	9134.12
FP22-death	9234
Death administration	94...00
Administration after pat. died	94...11
Death certificate form Med A	941..00
Death cert. Med A due	9411
Death cert. Med A signed	9412
Med A given to family	9413
Med A not signed-coroner case	9414
Death cert. Med A NOS	941Z.00
Medical cert. of still-birth	942..00

Report for Coroner	943..00
Coroner's post-mortem report	944..00
Hospital death discharge notif	945..00
Death notif. from hospital	9451
Await hosp death disch letter	9452
Receiv hosp death disch letter	9453
Ask for hosp death disch lett.	9454
Hospital death disch. NOS	945Z.00
Death notif.- non.hosp source	946..00
Cause of death clarif. SD17/18	947..00
SD17 - cause of death clarif	947..11
SD18 - cause of death clarif	947..12
SD17/18 received-death clarif.	9471
SD17/18 completed	9472
SD17/18-no details, returned	9473
SD17/18 cause of death NOS	947Z.00
Cremation certification	948..00
Stat B,C and F cremation certs	948..11
Patient died - to record place	949..00
Dead - place patient died	949..11
Deceased - place patient died	949..12
Died - place patient died	949..13
Place of death	949..14
Patient died at home	9491
Patient died in part 3 accom.	9492
Patient died in nursing home	9493
Patient died in resid.inst.NOS	9494
Patient died in hospital	9495
Patient died in street	9496
Patient died in publ.place NOS	9497
Dead on arrival at hospital	9498
Found dead at accident site	9499
Patient died in hospice	949A.00
Patient died in place NOS	949Z.00
Unexpected death-Coroner told	94A..00
Referral to coroner	94A..11
Cause of death	94B..00
Condition fatal-cause of death	94B..11
Post mortem report	94C..00
Hospital notified of death	94D..00
Death administration NOS	94Z..00
DEATH ANAESTHETIC	9681D
Sudden cardiac death, so described	G575100
Intrauterine death	L264.00
Fetal death in utero	L264.11
Intrauterine death unspecified	L264000

Intrauterine death - delivered	L264100
Intrauterine death with antenatal problem	L264200
Intrauterine death NOS	L264z00
Death obst cse occur more 42 day less than one yr aft deliv	L39A.00
Death from sequelae of direct obstetric causes	L39B.00
Obstetric death of unspecified cause	L39X.00
[X]Obstetric death of unspecified cause	Lyu7500
Fetal death due to prelabour anoxia	Q210.00
Fetal death due to labour anoxia	Q211.00
[X] Stillbirth	Q48D.00
Early neonatal death	Q48y600
Late neonatal death	Q48y700
Infant death	Q4z..11
Neonatal death	Q4z..12
Newborn death	Q4z..13
Perinatal death	Q4z..14
Stillbirth NEC	Q4z..15
[D]Mortality, cause unsure	R2...12
[D]Sudden death, cause unknown	R21..00
[D]Sudden infant death syndrome	R210.00
[D]Cot death	R210000
[D]Crib death	R210100
[D]Nonspecific sudden infant death	R210200
[D]Sudden infant death syndrome NOS	R210z00
[D]Instantaneous death	R211.00
[D]Death less than 24 hours from onset of illness	R212.00
[D]Death, not instantaneous cause unknown	R212000
[D]Died, with no sign of disease	R212100
[D]Death less than 24 hours from onset of illness NOS	R212z00
[D]Unattended death	R213.00
[D]Found after death, unknown cause of death	R213000
[D]Found dead	R213100
[D]Unattended death NOS	R213z00
[D]Sudden death, cause unknown NOS	R21z.00
[X]Ill-defined and unknown causes of mortality	RyuC.00
[X]Sudden infant death syndrome	RyuC000
[X]Other sudden death, cause unknown	RyuC100
[X]Other ill-defined and unspecified causes of death	RyuC200
Found dead on railway right-of-way unspecified	T0y0.00
Found dead on railway unspec - railway employee	T0y0000
Found dead on railway unspecified - passenger	T0y0100
Found dead on railway unspecified - pedestrian	T0y0200
Found dead on railway unspecified - cyclist	T0y0300
Found dead on railway unspecified - other spec person	T0y0y00
Found dead on railway unspecified - unspecified person	T0y0z00
DEATH	T140 F

DEATH AT HOME	T140 FH
DEATH IN HOSPITAL	T140 FP
POST MORTEM RESULT	T140 G
DIED	T1400M
SUDDEN INFANT DEATH	T1400SI
PATIENT DIED	T400
VIOLENT DEATH	T4001
SUDDEN DEATH	T4002
[V]Issue of death certificate	ZV68011

Appendix III-c Codes for alcohol use

Description	medcode	Assigned alcohol status
Teetotaller	1361	Non-drinker
Non drinker alcohol	1361.11	Non-drinker
Non-drinker alcohol	1361.12	Non-drinker
Current non drinker	136M.00	Non-drinker
NON-DRINKER ALCOHOL	L5154NI	Non-drinker
ALCOHOL NONE	L5154NO	Non-drinker
Alcohol consumption	136..00	Drinker
Drinks rarely	1362.11	Drinker
Drinks occasionally	1362.12	Drinker
Stopped drinking alcohol	1367	Drinker
Spirit drinker	136F.00	Drinker
Beer drinker	136G.00	Drinker
Drinks beer and spirits	136H.00	Drinker
Drinks wine	136I.00	Drinker
Social drinker	136J.00	Drinker
Alcohol intake within recommended sensible limits	136L.00	Drinker
Light drinker	136N.00	Drinker
Moderate drinker	136O.00	Drinker
Heavy drinker	136P.00	Drinker
Very heavy drinker	136Q.00	Drinker
Alcohol consumption NOS	136Z.00	Drinker
O/E - breath - alcohol smell	2577	Drinker
O/E - alcoholic breath	2577.11	Drinker
INTOXICATION ALCOHOL ACUTE	3039AC	Drinker
INTOXICATION ALCOHOL	3039AD	Drinker
PIXILLATED	3039AE	Drinker
HUNG OVER (HANGOVER)	3039HR	Drinker
ALCOHOL BINGES	3039PB	Drinker
Health ed. - alcohol	6792	Drinker
Pregnancy alcohol advice	67A5.00	Drinker
Patient advised about alcohol	8CAM.00	Drinker
Alcohol leaflet given	8CE1.00	Drinker
Referral to community alcohol team	8H7p.00	Drinker
INGESTION ALCOHOL	9890A	Drinker
Hangover (alcohol)	E250.12	Drinker
Inebriety NOS	E250.13	Drinker
Intoxication - alcohol	E250.14	Drinker
ADVISED TO STOP DRINKING	L2621ST	Drinker
ALCOHOL CONSUMPTION	L5150C	Drinker
ALCOHOL BEER	L5154B	Drinker
ALCOHOL MIXED WINE BEER & SPIRITS	L5154M	Drinker

ALCOHOL SPIRITS	L5154S	Drinker
ALCOHOL WINE	L5154W	Drinker
[D]Alcohol blood level excessive	R103.00	Drinker
HEAVY DRINKER	T514	Drinker
ALCOHOL RARELY	T5151	Drinker
ALCOHOL MODERATE	T5152	Drinker
ALCOHOL OCCASIONALLY	T5153	Drinker
SOCIAL DRINKER ALCOHOL	T5154	Drinker
STOPPED DRINKING ALCOHOL	T5156	Drinker
Planned reduction of alcohol consumption	Z191200	Drinker
Self-monitoring of alcohol intake	Z191400	Drinker
Removal of alcohol	Z9KF400	Drinker
Removing alcohol from home	Z9KF600	Drinker
Advice to change alcoholic drink intake	ZC22200	Drinker
Advice to change alcohol intake	ZC2H.00	Drinker
Advice on alcohol consumption	ZG23100	Drinker
[V] Alcohol use	ZV4KC00	Drinker
Ex-trivial drinker (<1u/day)	136A.00	Drinker
Ex-light drinker - (1-2u/day)	136B.00	Drinker
Ex-moderate drinker - (3-6u/d)	136C.00	Drinker
Ex-heavy drinker - (7-9u/day)	136D.00	Drinker
Ex-very heavy drinker-(>9u/d)	136E.00	Drinker
Trivial drinker - <1u/day	1362	Drinker
Light drinker - 1-2u/day	1363	Drinker
Moderate drinker - 3-6u/day	1364	Drinker
Heavy drinker - 7-9u/day	1365	Drinker
Very heavy drinker - >9u/day	1366	Drinker
Alcohol intake above recommended sensible limits	136K.00	Alcoholic
Alcoholics anonymous	13Y8.00	Alcoholic
H/O: alcoholism	1462	Alcoholic
ALCOHOL DRINKING EXCESSIVE	3031	Alcoholic
ALCOHOL ADDICTION	3032	Alcoholic
SYMPTOMS ALCOHOLIC WITHDRAWAL	3032B	Alcoholic
ALCOHOL DEPENDENCE	3032D	Alcoholic
ALCOHOL ABUSE INTOXICATION CHRONIC	3032NA	Alcoholic
INTOXICATION ALCOHOL CHRONIC	3032NB	Alcoholic
ABUSE ALCOHOL	3032NC	Alcoholic
WINE ADDICTION	3032WN	Alcoholic
ALCOHOLISM	3039A	Alcoholic
ABSINTHISM	3039AB	Alcoholic
PROBLEMS ALCOHOL RELATED	3039AP	Alcoholic
FALLS ALCOHOLIC	3039FL	Alcoholic
ALCOHOL ABUSE	3039PA	Alcoholic
PROBLEM DRINKING STRAIN ON SPOUSE	3039PP	Alcoholic
PROBLEM DRINKING (ALCOHOL)	3039PR	Alcoholic
CIRRHOSIS ALCOHOLIC	5710CA	Alcoholic

SICKNESS AFTER ALCOHOL ABUSE	7841LA	Alcoholic
Alcohol detoxification	8BA8.00	Alcoholic
Admitted to alcohol detoxification centre	8H35.00	Alcoholic
Under care of community alcohol team	9NN2.00	Alcoholic
Pathological alcohol intoxication	E014.00	Alcoholic
Drunkenness - pathological	E014.11	Alcoholic
Alcohol dependence syndrome	E23..00	Alcoholic
Alcoholism	E23..11	Alcoholic
Alcohol problem drinking	E23..12	Alcoholic
Alcohol dependence with acute alcoholic intoxication	E230.11	Alcoholic
Continuous acute alcoholic intoxication in alcoholism	E230100	Alcoholic
Episodic acute alcoholic intoxication in alcoholism	E230200	Alcoholic
Chronic alcoholism	E231.00	Alcoholic
Dipsomania	E231.11	Alcoholic
Unspecified chronic alcoholism	E231000	Alcoholic
Continuous chronic alcoholism	E231100	Alcoholic
Episodic chronic alcoholism	E231200	Alcoholic
Chronic alcoholism in remission	E231300	Alcoholic
Chronic alcoholism NOS	E231z00	Alcoholic
Alcohol dependence syndrome NOS	E23z.00	Alcoholic
Nondependent alcohol abuse	E250.00	Alcoholic
Drunkenness NOS	E250.11	Alcoholic
Nondependent alcohol abuse, unspecified	E250000	Alcoholic
Nondependent alcohol abuse, continuous	E250100	Alcoholic
Nondependent alcohol abuse, episodic	E250200	Alcoholic
Nondependent alcohol abuse in remission	E250300	Alcoholic
Nondependent alcohol abuse NOS	E250z00	Alcoholic
[X]Acute alcoholic drunkenness	Eu10011	Alcoholic
[X]Alcohol addiction	Eu10211	Alcoholic
[X]Chronic alcoholism	Eu10212	Alcoholic
[X]Dipsomania	Eu10213	Alcoholic
Alcoholic cirrhosis of the liver	J612.00	Alcoholic
HIGH RISK ALCOHOLISM	T185	Alcoholic
ALCOHOLICS ANONYMOUS ATTENDED	T3810	Alcoholic
DETOXIFICATION ALCOHOL	T3821	Alcoholic
Alcohol detoxification	Z191.00	Alcoholic
Drying out	Z191111	Alcoholic
Alcohol reduction programme	Z191211	Alcoholic
Alcoholism counselling	Z4B1.00	Alcoholic
[V]Personal history of alcoholism	ZV11300	Alcoholic
[V]Problems related to lifestyle alcohol use	ZV11311	Alcoholic
[V]Alcohol rehabilitation	ZV57A00	Alcoholic
[V]Alcohol abuse counselling and surveillance	ZV6D600	Alcoholic
SHAKES ALCOHOLIC	2910	Problem drinker
KORSAKOV'S PSYCHOSIS ALCOHOLIC	2911	Problem drinker

HALLUCINATIONS ALCOHOLIC	2912	Problem drinker
ALCOHOLIC PSYCHOSIS PARANOID	2913	Problem drinker
DEMENTIA ALCOHOLIC	2919	Problem drinker
PSYCHOSIS ALCOHOLIC	2919P	Problem drinker
ALCOHOLIC CARDIOPATHY	3032C	Problem drinker
EPILEPSY ALCOHOLIC	3032EP	Problem drinker
ALCOHOLIC GASTRITIS	3032G	Problem drinker
ALCOHOLIC GASTRITIS CHRONIC	3032GC	Problem drinker
NEUROPATHY ALCOHOLIC	3032R	Problem drinker
ALCOHOL RELATED DISTURBANCES	3039AR	Problem drinker
ALCOHOLIC GASTRITIS ACUTE	3039G	Problem drinker
POLYNEURITIS ALCOHOLIC	3039PN	Problem drinker
HEPATITIS ALCOHOLIC	5710HA	Problem drinker
MICRONODULAR CIRRHOSIS	5710MC	Problem drinker
Alcohol-induced pseudo-Cushing's syndrome	C150500	Problem drinker
Alcoholic psychoses	E01..00	Problem drinker
Alcohol withdrawal delirium	E010.00	Problem drinker
Alcohol amnestic syndrome	E011.00	Problem drinker
Korsakov's alcoholic psychosis	E011000	Problem drinker
Korsakov's alcoholic psychosis with peripheral neuritis	E011100	Problem drinker
Alcohol amnestic syndrome NOS	E011z00	Problem drinker
Other alcoholic dementia	E012.00	Problem drinker
Alcoholic dementia NOS	E012.11	Problem drinker
Chronic alcoholic brain syndrome	E012000	Problem drinker
Alcohol withdrawal hallucinosis	E013.00	Problem drinker
Alcoholic paranoia	E015.00	Problem drinker
Other alcoholic psychosis	E01y.00	Problem drinker
Alcohol withdrawal syndrome	E01y000	Problem drinker
Other alcoholic psychosis NOS	E01yz00	Problem drinker
Alcoholic psychosis NOS	E01z.00	Problem drinker
Acute alcoholic intoxication in alcoholism	E230.00	Problem drinker
Acute alcoholic intoxication, unspecified, in alcoholism	E230000	Problem drinker
Acute alcoholic intoxication in remission, in alcoholism	E230300	Problem drinker
Acute alcoholic intoxication in alcoholism NOS	E230z00	Problem drinker
[X]Mental and behavioural disorders due to use of alcohol	Eu10.00	Problem drinker
[X]Mental & behav dis due to use alcohol: acute intoxication	Eu10000	Problem drinker
[X]Mental and behav dis due to use of alcohol: harmful use	Eu10100	Problem drinker
[X]Mental and behav dis due to use alcohol: dependence syndr	Eu10200	Problem drinker
[X]Mental and behav dis due to use alcohol: withdrawal state	Eu10300	Problem drinker
[X]Men & behav dis due alcohl: withdrawl state	Eu10400	Problem drinker

with delirium		
[X]Delirium tremens, alcohol induced	Eu10411	Problem drinker
[X]Mental & behav dis due to use alcohol: psychotic disorder	Eu10500	Problem drinker
[X]Alcoholic hallucinosis	Eu10511	Problem drinker
[X]Alcoholic jealousy	Eu10512	Problem drinker
[X]Alcoholic paranoia	Eu10513	Problem drinker
[X]Alcoholic psychosis NOS	Eu10514	Problem drinker
[X]Mental and behav dis due to use alcohol: amnesic syndrome	Eu10600	Problem drinker
[X]Korsakov's psychosis, alcohol induced	Eu10611	Problem drinker
[X]Men & behav dis due alcoh: resid & late-onset psychot dis	Eu10700	Problem drinker
[X]Alcoholic dementia NOS	Eu10711	Problem drinker
[X]Chronic alcoholic brain syndrome	Eu10712	Problem drinker
[X]Men & behav dis due to use alcohol: oth men & behav dis	Eu10y00	Problem drinker
[X]Ment & behav dis due use alcohol: unsp ment & behav dis	Eu10z00	Problem drinker
Cerebral degeneration due to alcoholism	F11x000	Problem drinker
Alcoholic encephalopathy	F11x011	Problem drinker
Cerebellar ataxia due to alcoholism	F144000	Problem drinker
Alcoholic polyneuropathy	F375.00	Problem drinker
Alcoholic myopathy	F394100	Problem drinker
Alcoholic cardiomyopathy	G555.00	Problem drinker
Alcoholic gastritis	J153.00	Problem drinker
Alcoholic fatty liver	J610.00	Problem drinker
Acute alcoholic hepatitis	J611.00	Problem drinker
Alcoholic cirrhosis of liver	J612.00	Problem drinker
Alcoholic fibrosis and sclerosis of liver	J612000	Problem drinker
Alcoholic liver damage unspecified	J613.00	Problem drinker
Alcoholic hepatic failure	J613000	Problem drinker
Alcoholic hepatitis	J617.00	Problem drinker
Chronic alcoholic hepatitis	J617000	Problem drinker
Alcohol-induced chronic pancreatitis	J671000	Problem drinker
Alcohol causing toxic effect	SM0..00	Problem drinker
Alcohol causing toxic effect NOS	SM0z.00	Problem drinker
Alcohol withdrawal regime	Z191100	Problem drinker

Appendix III-d Codes for viral hepatitis

description	medcode
HERPES VIRUS HEPATITIS	054 H
VIRUS HEPATITIS TYPE A	070 A
HEPATITIS C	070 AC
HEPATITIS TYPE C	070 AD
VIRUS HEPATITIS TYPE B	070 B
HEPATITIS TYPE NON- A NON- B	070 N
VIRUS HEPATITIS	070 RL
HEPATITIS COXSACKIE VIRUS	0749H
HEPATITIS ADENOVIRUS	0788H
HEPATITIS CYTOMEGALIC INCLUSION VIRUS	0795H
Hepatitis C status	2J1..00
Hepatitis A status	2J2..00
Hepatitis A - current infection	2J23.00
Hepatitis B antibody present	43B2.11
Hepatitis B surface antig +ve	43B4.00
Hepatitis e antigen present	43B5.00
Hepatitis A test positive	43M2.00
Hepatitis C antibody test positive	43X3.00
Viral hepatitis carrier	65Q7.00
Viral hepatitis	A70..00
Viral hepatitis A with coma	A700.00
Viral (infectious) hepatitis A	A701.00
Viral hepatitis B with coma	A702.00
Viral (serum) hepatitis B	A703.00
Other specified viral hepatitis with coma	A704.00
Viral hepatitis C with coma	A704000
Other specified viral hepatitis with hepatic coma NOS	A704z00
Other specified viral hepatitis without coma	A705.00
Viral hepatitis C without mention of hepatic coma	A705000
Acute delta-(super)infection of hepatitis B carrier	A705100
Acute hepatitis E	A705200
Hepatitis non A non B	A705400
Other specified viral hepatitis without mention of coma NOS	A705z00
Unspecified viral hepatitis with coma	A706.00
Chronic viral hepatitis	A707.00
Chronic viral hepatitis B with delta-agent	A707000
Chronic viral hepatitis B without delta-agent	A707100
Chronic viral hepatitis C	A707200
Chronic viral hepatitis, unspecified	A707X00
Unspecified viral hepatitis	A70z.00
Hepatitis C	A70z000
Cytomegaloviral hepatitis	A785200
[X]Viral hepatitis	AyuB.00

[X]Other specified acute viral hepatitis	AyuB000
[X]Other chronic viral hepatitis	AyuB100
[X]Chronic viral hepatitis, unspecified	AyuB200
[X]Unspecified viral hepatitis with coma	AyuB300
[X]Unspecified viral hepatitis without coma	AyuB400
Hepatitis in viral diseases EC	J631.00
Hepatitis in coxsackie virus	J631000
Hepatitis in cytomegalic inclusion virus	J631100
Hepatitis in other viral disease	J631500
Hepatitis in viral diseases EC NOS	J631z00
Viral hepatitis comp pregnancy, childbirth & the puerperium	L176500
ANTIBODIES HEPATITIS B CORE PRESENT	L6652DV
ANTIBODIES HEPATITIS B E PRESENT	L6652DW
ANTIBODIES HEPATITIS SURFACE PRESENT	L6652DX
ANTIBODIES HEPATITIS E PRESENT	L6652DY
Congenital viral hepatitis	Q409.00
Congenital hepatitis A infection	Q409000
Congenital hepatitis B infection	Q409100
Other specified congenital viral hepatitis	Q409y00
Congenital viral hepatitis NOS	Q409z00
[V]Hepatitis B carrier	ZV02B00

Appendix III-e Codes for autoimmune liver disease

Description	medcode
PRIMARY BILIARY CIRRHOSIS (LIVER)	5719PB
SCLEROSING CHOLANGITIS PRIMARY	575 AL
Autoimmune chronic active hepatitis	J614111
Primary biliary cirrhosis	J616000
Primary sclerosing cholangitis	J661700

Appendix III-f Codes for metabolic liver disease

Description	medcode
HAEMOCHROMATOSIS	2732
DIABETES BRONZE (HAEMOCHROMATOSIS)	2732B
HAEMOCHROMATOSIS IDIOPATHIC	2732HI
WILSON'S DISEASE	2733W
ANTITRYPSIN DEFICIENCY	2790AD
Alpha-1-antitrypsin phenotype	4L00.00
Haemochromatosis	C350000
Bronzed diabetes	C350011
Von Recklinghausen - Applebaum disease	C350013
Hepatolenticular degeneration (Wilson's disease)	C351000
Wilson's disease	C351011
Alpha-1-antitrypsin hepatitis	C376100
Alpha-1-antitrypsin deficiency	C376200

Appendix III-g Codes for encephalopathy

description	medcode
WERNICKE'S ENCEPHALOPATHY	2639WN
ENCEPHALOPATHY	7817
Wernicke's encephalopathy	C251.11
Wernicke's encephalopathy	C253.00
Alcoholic encephalopathy	F11x011
Unspecified encephalopathy	F283.00
Hepatic coma	J622.00
Encephalopathy - hepatic	J622.11
Hepatorenal syndrome	J624.00
[X] Hepatic failure	J625.00
[X] Liver failure	J625.11
Liver failure NOS	J62y.12
Hepatic failure	J62y.13
Bilirubin encephalopathy	Q437000

Appendix III-h Codes for smoking

Description	medcode	Assigned smoking status
Never smoked tobacco	1371	Non-smoker
Non-smoker	1371.11	Non-smoker
Current non-smoker	137L.00	Non-smoker
SMOKER NON	T5093	Non-smoker
SMOKED NEVER	T5093N	Non-smoker
Ex-trivial smoker (<1/day)	1377	Ex-Smoker
Ex-light smoker (1-9/day)	1378	Ex-Smoker
Ex-moderate smoker (10-19/day)	1379	Ex-Smoker
Ex-heavy smoker (20-39/day)	137A.00	Ex-Smoker
Ex-very heavy smoker (40+/day)	137B.00	Ex-Smoker
Ex-smoker - amount unknown	137F.00	Ex-Smoker
Stopped smoking	137K.00	Ex-Smoker
Ex pipe smoker	137N.00	Ex-Smoker
Ex cigar smoker	137O.00	Ex-Smoker
Ex smoker	137S.00	Ex-Smoker
Date ceased smoking	137T.00	Ex-Smoker
Smoking free weeks	13p4.00	Ex-Smoker
[X]Mental and behav dis due to use tobacco: withdrawal state	Eu17300	Ex-Smoker
[X]Men & behav dis due tobacco: withdrawl state wth delirium	Eu17400	Ex-Smoker
STOPPED SMOKING	T5091	Ex-Smoker
FORMER SMOKER	T5091ES	Ex-Smoker
EX HEAVY SMOKER	T5091HS	Ex-Smoker
Smoker - amount smoked	137..11	Smoker
Trivial smoker - < 1 cig/day	1372	Smoker
Occasional smoker	1372.11	Smoker
Light smoker - 1-9 cigs/day	1373	Smoker
Moderate smoker - 10-19 cigs/d	1374	Smoker
Heavy smoker - 20-39 cigs/day	1375	Smoker
Very heavy smoker - 40+cigs/d	1376	Smoker
Keeps trying to stop smoking	137C.00	Smoker
Trying to give up smoking	137G.00	Smoker
Pipe smoker	137H.00	Smoker
Cigar smoker	137J.00	Smoker
Rolls own cigarettes	137M.00	Smoker
Cigarette smoker	137P.00	Smoker
Smoker	137P.11	Smoker
Smoking started	137Q.00	Smoker
Smoking restarted	137Q.11	Smoker
Current smoker	137R.00	Smoker
Smoking reduced	137V.00	Smoker

Cigarette consumption	137X.00	Smoker
Cigar consumption	137Y.00	Smoker
Tobacco consumption NOS	137Z.00	Smoker
Pipe tobacco consumption	137a.00	Smoker
Ready to stop smoking	137b.00	Smoker
Thinking about stopping smoking	137c.00	Smoker
Not interested in stopping smoking	137d.00	Smoker
Smoking restarted	137e.00	Smoker
Reason for restarting smoking	137f.00	Smoker
Negotiated date for cessation of smoking	13p0.00	Smoker
Smoking cessation programme start date	13p5.00	Smoker
Health ed. - smoking	6791	Smoker
Smoking cessation advice	8CAL.00	Smoker
Referral to smoking cessation advisor	8H7i.00	Smoker
Seen by smoking cessation advisor	9N2k.00	Smoker
Attends stop smoking monitor.	9OO1.00	Smoker
Refuses stop smoking monitor	9OO2.00	Smoker
Stop smoking monitor verb.inv.	9OO7.00	Smoker
Stop smoking monitor phone inv	9OO8.00	Smoker
Tobacco dependence	E251.00	Smoker
Tobacco dependence, unspecified	E251000	Smoker
Tobacco dependence, continuous	E251100	Smoker
Tobacco dependence, episodic	E251200	Smoker
Tobacco dependence in remission	E251300	Smoker
Tobacco dependence NOS	E251z00	Smoker
[X]Mental and behavioural disorder due to use of tobacco	Eu17.00	Smoker
[X]Mental and behav dis due to use of tobacco: harmful use	Eu17100	Smoker
[X]Mental and behav dis due to use tobacco: dependence syndr	Eu17200	Smoker
[X]Mental & behav dis due to use tobacco: psychotic disorder	Eu17500	Smoker
[X]Mental and behav dis due to use tobacco: amnesic syndrome	Eu17600	Smoker
[X]Men & beh dis due tobacco: resid & late-onset psychot dis	Eu17700	Smoker
[X]Men & behav dis due to use tobacco: oth men & behav dis	Eu17y00	Smoker
[X]Ment & behav dis due use tobacco: unsp ment & behav dis	Eu17z00	Smoker
SMOKING STARTED	L5091S	Smoker
Toxic effect of tobacco and nicotine	SMC..00	Smoker
SMOKER	T509	Smoker
SMOKING RESTARTED	T509 SR	Smoker
SMOKER OWN ROLLED	T5090OR	Smoker
SMOKER CIGARETTES	T5090XC	Smoker
SMOKING ADVISED TO STOP	T5092	Smoker

SMOKING WISHES TO STOP	T5092S	Smoker
SMOKING WANTS TO STOP	T5092SA	Smoker
EXCESSIVE SMOKING	T510	Smoker
HEAVY SMOKER (20-PLUS PER DAY)	T510 HS	Smoker
SMOKING EXCESSIVE	T510 SE	Smoker
SMOKER HEAVY (Ex-Smoker0-PLUS PER DAY)	T510 SH	Smoker
SMOKER MODERATE (LESS THAN 20 PER DAY)	T511	Smoker
SMOKER (20 PER DAY)	T5112	Smoker
SMOKER (15 PER DAY)	T5113	Smoker
SMOKER (10 PER DAY)	T5114	Smoker
SMOKER (LESS THAN 10 PER DAY)	T5115	Smoker
SMOKER MILD (5 OR LESS PER DAY)	T5115M	Smoker
SMOKER(OCCASIONAL)	T5116	Smoker
SMOKER (30 PER DAY)	T5117	Smoker
SMOKER PIPE	T512	Smoker
SMOKER CIGARS	T513	Smoker
[V]Tobacco use	ZV4K000	Smoker
[V]Tobacco abuse counselling	ZV6D800	Smoker
Tobacco consumption	137..00	Unknown
Tobacco consumption unknown	137E.00	Unknown

Appendix III-j Codes for comorbidity

Table j-i Codes for myocardial infarct

description	medcode
H/O: myocardial infarct <60	14A3.00
H/O: myocardial infarct >60	14A4.00
H/O: angina pectoris	14A5.00
H/O: heart disease NOS	14AA.00
H/O: Myocardial infarction in last year	14AH.00
H/O: Angina in last year	14AJ.00
H/O: atrial fibrillation	14AN.00
H/O: CVS disease NOS	14AZ.00
Special CVS test abnormal	3154
ECG: myocardial ischaemia	322..00
ECG:shows myocardial ischaemia	3222
ECG: myocardial ischaemia NOS	322Z.00
ECG: myocardial infarction	323..00
ECG: old myocardial infarction	3232
ECG: antero-septal infarct.	3233
ECG:posterior/inferior infarct	3234
ECG: subendocardial infarct	3235
ECG: lateral infarction	3236
ECG: myocardial infarct NOS	323Z.00
ECG: heart block	329..00
Acute myocardial infarction	G30..00
Attack - heart	G30..11
Coronary thrombosis	G30..12
Cardiac rupture following myocardial infarction (MI)	G30..13
Heart attack	G30..14
MI - acute myocardial infarction	G30..15
Thrombosis - coronary	G30..16
Silent myocardial infarction	G30..17
Acute anterolateral infarction	G300.00
Other specified anterior myocardial infarction	G301.00
Acute anteroapical infarction	G301000
Acute anteroseptal infarction	G301100
Anterior myocardial infarction NOS	G301z00
Acute inferolateral infarction	G302.00
Acute inferoposterior infarction	G303.00
Posterior myocardial infarction NOS	G304.00
Lateral myocardial infarction NOS	G305.00
True posterior myocardial infarction	G306.00
Acute subendocardial infarction	G307.00
Acute non-Q wave infarction	G307000
Acute non-ST segment elevation myocardial infarction	G307100
Inferior myocardial infarction NOS	G308.00
Acute Q-wave infarct	G309.00

Mural thrombosis	G30A.00
Acute posterolateral myocardial infarction	G30B.00
Acute transmural myocardial infarction of unspecif site	G30X.00
Acute ST segment elevation myocardial infarction	G30X000
Other acute myocardial infarction	G30y.00
Acute atrial infarction	G30y000
Acute papillary muscle infarction	G30y100
Acute septal infarction	G30y200
Other acute myocardial infarction NOS	G30yz00
Acute myocardial infarction NOS	G30z.00
Other acute and subacute ischaemic heart disease	G31..00
Postmyocardial infarction syndrome	G310.00
Dressler's syndrome	G310.11
Preinfarction syndrome	G311.00
Crescendo angina	G311.11
Impending infarction	G311.12
Unstable angina	G311.13
Angina at rest	G311.14
Unstable angina	G311100
Angina at rest	G311200
Refractory angina	G311300
Worsening angina	G311400
Acute coronary syndrome	G311500
Preinfarction syndrome NOS	G311z00
Coronary thrombosis not resulting in myocardial infarction	G312.00
Other acute and subacute ischaemic heart disease	G31y.00
Acute coronary insufficiency	G31y000
Microinfarction of heart	G31y100
Subendocardial ischaemia	G31y200
Transient myocardial ischaemia	G31y300
Other acute and subacute ischaemic heart disease NOS	G31yz00
Old myocardial infarction	G32..00
Healed myocardial infarction	G32..11
Personal history of myocardial infarction	G32..12
Angina pectoris	G33..00
Status anginosus	G33z000
Stenocardia	G33z100
Syncope anginosa	G33z200
Angina on effort	G33z300
Ischaemic chest pain	G33z400
Post infarct angina	G33z500
New onset angina	G33z600
Stable angina	G33z700
Angina pectoris NOS	G33zz00
Other chronic ischaemic heart disease	G34..00
Coronary atherosclerosis	G340.00

Triple vessel disease of the heart	G340.11
Coronary artery disease	G340.12
Aneurysm of heart	G341.00
Cardiac aneurysm	G341.11
Atherosclerotic cardiovascular disease	G342.00
Ischaemic cardiomyopathy	G343.00
Silent myocardial ischaemia	G344.00
Other specified chronic ischaemic heart disease	G34y.00
Chronic coronary insufficiency	G34y000
Chronic myocardial ischaemia	G34y100
Other specified chronic ischaemic heart disease NOS	G34yz00
Other chronic ischaemic heart disease NOS	G34z.00
Subsequent myocardial infarction	G35..00
Subsequent myocardial infarction of anterior wall	G350.00
Subsequent myocardial infarction of inferior wall	G351.00
Subsequent myocardial infarction of other sites	G353.00
Subsequent myocardial infarction of unspecified site	G35X.00
Certain current complication follow acute myocardial infarct	G36..00
Haemopericardium/current comp folow acut myocard infarct	G360.00
Atrial septal defect/curr comp folow acut myocardal infarct	G361.00
Ventric septal defect/curr comp fol acut myocardal infarctn	G362.00
Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	G363.00
Ruptur chordae tendinae/curr comp fol acute myocard infarct	G364.00
Rupture papillary muscle/curr comp fol acute myocard infarct	G365.00
Thrombosis atrium,auric append&vent/curr comp foll acute MI	G366.00
Postoperative myocardial infarction	G38..00
Postoperative transmural myocardial infarction anterior wall	G380.00
Postoperative transmural myocardial infarction inferior wall	G381.00
Postoperative transmural myocardial infarction other sites	G382.00
Postoperative transmural myocardial infarction unspec site	G383.00
Postoperative subendocardial myocardial infarction	G384.00
Postoperative myocardial infarction, unspecified	G38z.00
Other specified ischaemic heart disease	G3y..00
Ischaemic heart disease NOS	G3z..00
Acute cor pulmonale	G400.00
Acute pericarditis in diseases EC	G500.00
Post infarction pericarditis	G501.00
Other and unspecified acute pericarditis	G50z.00
Rupture of papillary muscle	G5y6.00
[X]Other current complicatns following acute myocard infarct	Gyu3100
[X]Acute transmural myocardial infarction of unspecif site	Gyu3400
[X]Subsequent myocardial infarction of other sites	Gyu3500
[X]Subsequent myocardial infarction of unspecified site	Gyu3600

Table j-ii Codes for Congestive heart failure

description	medcode
Suspected heart failure	1J60.00
Heart failure confirmed	1O1..00
O/E - pulmonary oedema	23E1.00
New York Heart Assoc classification heart failure symptoms	388D.00
New York Heart Association classification - class I	662f.00
New York Heart Association classification - class II	662g.00
New York Heart Association classification - class III	662h.00
New York Heart Association classification - class IV	662i.00
Malignant hypertensive heart disease with CCF	G210100
Benign hypertensive heart disease with CCF	G211100
Hypertensive heart disease NOS with CCF	G21z100
Hypertensive heart&renal dis wth (congestive) heart failure	G232.00
Hyperten heart&renal dis+both(congestv)heart and renal fail	G234.00
Aneurysm of heart	G341.00
Congestive cardiomyopathy	G554000
Congestive obstructive cardiomyopathy	G554011
Heart failure	G58..00
Cardiac failure	G58..11
Congestive heart failure	G580.00
Congestive cardiac failure	G580.11
Right heart failure	G580.12
Right ventricular failure	G580.13
Biventricular failure	G580.14
Acute congestive heart failure	G580000
Chronic congestive heart failure	G580100
Left ventricular failure	G581.00
Pulmonary oedema - acute	G581.12
Acute heart failure	G582.00
Heart failure NOS	G58z.00
Cardiac failure NOS	G58z.12
Pulmonary oedema NOS	H541z00
Acute pulmonary oedema unspecified	H584.00
Acute oedema of lung, unspecified	H584.11
Acute pulmonary oedema NOS	H584z00
[D]Dropsy	R023200
Heart failure as a complication of care	SP11111
New York Heart Assoc classification heart failure symptoms	ZRad.00

Table j-iii Codes for Peripheral vascular disease

description	medcode
Diabetes mellitus with peripheral circulatory disorder	C107.00
Diabetes mellitus, juvenile +peripheral circulatory disorder	C107000
Diabetes mellitus, adult, + peripheral circulatory disorder	C107100
IDDM with peripheral circulatory disorder	C107300
NIDDM with peripheral circulatory disorder	C107400
Diabetes mellitus NOS with peripheral circulatory disorder	C107z00
Insulin dependent diab mell with peripheral angiopathy	C108G00
Type I diabetes mellitus with peripheral angiopathy	C108G11
Type 1 diabetes mellitus with peripheral angiopathy	C108G12
Non-insulin-dependent d m with peripheral angiopath	C109F00
Type II diabetes mellitus with peripheral angiopathy	C109F11
Type 2 diabetes mellitus with peripheral angiopathy	C109F12
Type 1 diabetes mellitus with peripheral angiopathy	C10EG00
Type I diabetes mellitus with peripheral angiopathy	C10EG11
Insulin dependent diab mell with peripheral angiopathy	C10EG12
Type 2 diabetes mellitus with peripheral angiopathy	C10FF00
Type II diabetes mellitus with peripheral angiopathy	C10FF11
Pulmonary arteritis	G42y000
Pulmonary vessel rupture	G42y100
Pulmonary vessel stricture	G42y200
Other specified pulmonary circulation disease NOS	G42yz00
Cardiovascular arteriosclerosis unspecified	G5y2.00
Arteriosclerosis	G70..11
Aorto-iliac disease	G700.11
Renal artery atherosclerosis	G701.00
Extremity artery atheroma	G702.00
Monckeberg's medial sclerosis	G702000
Other specified artery atheroma	G70y.00
Carotid artery atherosclerosis	G70y000
Arteriosclerotic vascular disease NOS	G70z.00
Other aneurysm	G72..00
Other peripheral vascular disease	G73..00
Peripheral ischaemic vascular disease	G73..11
Ischaemia of legs	G73..12
Peripheral ischaemia	G73..13
Buerger's disease	G731000
Peripheral gangrene	G732.00
Other specified peripheral vascular disease	G73y.00
Diabetic peripheral angiopathy	G73y000
Erythrocyanosis	G73y700
Spasm of peripheral artery	G73z100
Arterial embolism and thrombosis	G74..00
Arterial embolus and thrombosis	G74..11

Thrombosis - arterial	G74..12
Arterial embolic and thrombotic occlusion	G74..13
Polyarteritis nodosa and allied conditions	G75..00
Polyarteritis nodosa	G750.00
Necrotising angiitis	G750.11
Wegener's granulomatosis	G754.00
Giant cell arteritis	G755.00
Cranial arteritis	G755000
Temporal arteritis	G755100
Horton's disease	G755200
Giant cell arteritis NOS	G755z00
Thrombotic microangiopathy	G756.00
Takayasu's disease	G757.00
Aortic arch arteritis	G757.11
Pulseless disease	G757.12
Churg-Strauss vasculitis	G758.00
Juvenile polyarteritis	G759.00
Necrotising vasculopathy, unspecified	G75X.00
Polyarteritis nodosa and allied conditions NOS	G75z.00
Other disorders of arteries and arterioles	G76..00
Acquired arteriovenous fistula	G760.00
Stricture of artery	G761.00
Rupture of artery	G762.00
Hyperplasia of renal artery	G763.00
Coeliac artery compression syndrome	G764.00
Marable's syndrome	G764.11
Necrosis of artery	G765.00
Arteritis unspecified	G766.00
Aortitis	G766.11
Aortitis - syphilitic	G767.00
Other disorders of arteries and arterioles	G768.00
Anterior spinal and vertebral artery compression syndromes	G769.00
Arterial insufficiency	G76A.00
Vasculitis	G76B.00
Disorders of arteries and arterioles NOS	G76z.00
Diseases of capillaries	G77..00
Other specified arterial, arteriole or capillary disease	G7y..00
Arterial, arteriole and capillary diseases NOS	G7z..00
Phlebosclerosis	G8yy200
[X]Atherosclerosis of other arteries	Gyu7000
[X]Other specified peripheral vascular diseases	Gyu7400
[X]Embolism and thrombosis of other arteries	Gyu7500
[X]Other specified disorders of arteries and arterioles	Gyu7600
[X]Other diseases of capillaries	Gyu7700
[X]Peripheral angiopathy in diseases classified elsewhere	Gyu7A00
[X]Oth disorders/arteries,arterioles+capillaries/diseases CE	Gyu7B00

Vascular insufficiency of the intestine	J42..00
Acute intestinal vascular insufficiency	J420.00
Acute intestinal vascular insufficiency NOS	J420z00
Chronic intestinal vascular insufficiency	J421.00
Chronic intestinal vascular insufficiency NOS	J421z00
Intestinal vascular insufficiency NOS	J42z.00
Vascular disorders of intestine	J577.00
Gastric antral vascular ectasia	J577100
[X]Other vascular disorders of intestine	Jyu5000
Vascular disorders of kidney	K138.00
Renal vascular disorders	K138.11
Renal vascular disorders NOS	K138z00
Vascular disorders of penis	K275.00
Penile vascular disorder NOS	K275z00
Male genital organ vascular diseases	K286.00
Male genital vascular diseases NOS	K286z00
Giant cell arteritis with polymyalgia rheumatica	N200.00
[X]Other conditions related to polyarteritis nodosa	Nyu4000
[X]Other giant cell arteritis	Nyu4100
[X]Other specified necrotizing vasculopathies	Nyu4200
[X]Necrotising vasculopathy, unspecified	Nyu4D00
Other peripheral vascular system anomalies	P76..00
Peripheral arterio-venous aneurysm	P766.00
Peripheral arterio-venous malformation	P766.11
Congenital peripheral aneurysm	P767.00
Congenital anomaly of peripheral vascular system OS	P76y.00
Other congenital anomaly of peripheral vascular system NOS	P76yz00
Peripheral vascular system anomaly NOS	P76z.00
Cerebrovascular system anomaly NOS	P7y0z00
Other cardiovascular system anomaly NOS	P7yz.00
Other cardiovascular system anomaly NOS	P7yzz00
[D]Failure of peripheral circulation	R055000
[D]Peripheral circulatory failure	R055011
Peripheral vascular complications of care	SP12.00
Peripheral vascular complications of care NOS	SP12z00

Table j-iv Codes for Cerebrovascular disease

description	medcode
Diabetes mellitus with peripheral circulatory disorder	C107.00
Diabetes mellitus, juvenile +peripheral circulatory disorder	C107000
Diabetes mellitus, adult, + peripheral circulatory disorder	C107100
IDDM with peripheral circulatory disorder	C107300
NIDDM with peripheral circulatory disorder	C107400
Diabetes mellitus NOS with peripheral circulatory disorder	C107z00
Insulin dependent diab mell with peripheral angiopathy	C108G00
Type I diabetes mellitus with peripheral angiopathy	C108G11
Type 1 diabetes mellitus with peripheral angiopathy	C108G12
Non-insulin-dependent d m with peripheral angiopath	C109F00
Type II diabetes mellitus with peripheral angiopathy	C109F11
Type 2 diabetes mellitus with peripheral angiopathy	C109F12
Type 1 diabetes mellitus with peripheral angiopathy	C10EG00
Type I diabetes mellitus with peripheral angiopathy	C10EG11
Insulin dependent diab mell with peripheral angiopathy	C10EG12
Type 2 diabetes mellitus with peripheral angiopathy	C10FF00
Type II diabetes mellitus with peripheral angiopathy	C10FF11
Pulmonary arteritis	G42y000
Pulmonary vessel rupture	G42y100
Pulmonary vessel stricture	G42y200
Other specified pulmonary circulation disease NOS	G42yz00
Cardiovascular arteriosclerosis unspecified	G5y2.00
Arteriosclerosis	G70..11
Aorto-iliac disease	G700.11
Renal artery atherosclerosis	G701.00
Extremity artery atheroma	G702.00
Monckeberg's medial sclerosis	G702000
Other specified artery atheroma	G70y.00
Carotid artery atherosclerosis	G70y000
Arteriosclerotic vascular disease NOS	G70z.00
Other aneurysm	G72..00
Other peripheral vascular disease	G73..00
Peripheral ischaemic vascular disease	G73..11
Ischaemia of legs	G73..12
Peripheral ischaemia	G73..13
Buerger's disease	G731000
Peripheral gangrene	G732.00
Other specified peripheral vascular disease	G73y.00
Diabetic peripheral angiopathy	G73y000
Erythrocyanosis	G73y700
Spasm of peripheral artery	G73z100
Arterial embolism and thrombosis	G74..00
Arterial embolus and thrombosis	G74..11

Thrombosis - arterial	G74..12
Arterial embolic and thrombotic occlusion	G74..13
Polyarteritis nodosa and allied conditions	G75..00
Polyarteritis nodosa	G750.00
Necrotising angiitis	G750.11
Wegener's granulomatosis	G754.00
Giant cell arteritis	G755.00
Cranial arteritis	G755000
Temporal arteritis	G755100
Horton's disease	G755200
Giant cell arteritis NOS	G755z00
Thrombotic microangiopathy	G756.00
Takayasu's disease	G757.00
Aortic arch arteritis	G757.11
Pulseless disease	G757.12
Churg-Strauss vasculitis	G758.00
Juvenile polyarteritis	G759.00
Necrotising vasculopathy, unspecified	G75X.00
Polyarteritis nodosa and allied conditions NOS	G75z.00
Other disorders of arteries and arterioles	G76..00
Acquired arteriovenous fistula	G760.00
Stricture of artery	G761.00
Rupture of artery	G762.00
Hyperplasia of renal artery	G763.00
Coeliac artery compression syndrome	G764.00
Marable's syndrome	G764.11
Necrosis of artery	G765.00
Arteritis unspecified	G766.00
Aortitis	G766.11
Aortitis - syphilitic	G767.00
Other disorders of arteries and arterioles	G768.00
Anterior spinal and vertebral artery compression syndromes	G769.00
Arterial insufficiency	G76A.00
Vasculitis	G76B.00
Disorders of arteries and arterioles NOS	G76z.00
Diseases of capillaries	G77..00
Other specified arterial, arteriole or capillary disease	G7y..00
Arterial, arteriole and capillary diseases NOS	G7z..00
Phlebosclerosis	G8yy200
[X]Atherosclerosis of other arteries	Gyu7000
[X]Other specified peripheral vascular diseases	Gyu7400
[X]Embolism and thrombosis of other arteries	Gyu7500
[X]Other specified disorders of arteries and arterioles	Gyu7600
[X]Other diseases of capillaries	Gyu7700
[X]Peripheral angiopathy in diseases classified elsewhere	Gyu7A00
[X]Oth disorders/arteries,arterioles+capillaries/diseases CE	Gyu7B00

Vascular insufficiency of the intestine	J42..00
Acute intestinal vascular insufficiency	J420.00
Acute intestinal vascular insufficiency NOS	J420z00
Chronic intestinal vascular insufficiency	J421.00
Chronic intestinal vascular insufficiency NOS	J421z00
Intestinal vascular insufficiency NOS	J42z.00
Vascular disorders of intestine	J577.00
Gastric antral vascular ectasia	J577100
[X]Other vascular disorders of intestine	Jyu5000
Vascular disorders of kidney	K138.00
Renal vascular disorders	K138.11
Renal vascular disorders NOS	K138z00
Vascular disorders of penis	K275.00
Penile vascular disorder NOS	K275z00
Male genital organ vascular diseases	K286.00
Male genital vascular diseases NOS	K286z00
Giant cell arteritis with polymyalgia rheumatica	N200.00
[X]Other conditions related to polyarteritis nodosa	Nyu4000
[X]Other giant cell arteritis	Nyu4100
[X]Other specified necrotizing vasculopathies	Nyu4200
[X]Necrotising vasculopathy, unspecified	Nyu4D00
Other peripheral vascular system anomalies	P76..00
Peripheral arterio-venous aneurysm	P766.00
Peripheral arterio-venous malformation	P766.11
Congenital peripheral aneurysm	P767.00
Congenital anomaly of peripheral vascular system OS	P76y.00
Other congenital anomaly of peripheral vascular system NOS	P76yz00
Peripheral vascular system anomaly NOS	P76z.00
Cerebrovascular system anomaly NOS	P7y0z00
Other cardiovascular system anomaly NOS	P7yz.00
Other cardiovascular system anomaly NOS	P7yzz00
[D]Failure of peripheral circulation	R055000
[D]Peripheral circulatory failure	R055011
Peripheral vascular complications of care	SP12.00
Peripheral vascular complications of care NOS	SP12z00

Table j-v Codes for Dementia

description	medcode
H/O: dementia	1461
Senile dementia	E00..11
Senile/presenile dementia	E00..12
Uncomplicated senile dementia	E000.00
Presenile dementia	E001.00
Uncomplicated presenile dementia	E001000
Presenile dementia with delirium	E001100
Presenile dementia with paranoia	E001200
Presenile dementia with depression	E001300
Presenile dementia NOS	E001z00
Senile dementia with depressive or paranoid features	E002.00
Senile dementia with paranoia	E002000
Senile dementia with depression	E002100
Senile dementia with depressive or paranoid features NOS	E002z00
Senile dementia with delirium	E003.00
Arteriosclerotic dementia	E004.00
Multi infarct dementia	E004.11
Uncomplicated arteriosclerotic dementia	E004000
Arteriosclerotic dementia with delirium	E004100
Arteriosclerotic dementia with paranoia	E004200
Arteriosclerotic dementia with depression	E004300
Arteriosclerotic dementia NOS	E004z00
Dementia in conditions EC	E041.00
Chronic confusional state	E042.00
[X]Dementia in Alzheimer's disease	Eu00.00
[X]Dementia in Alzheimer's disease with early onset	Eu00000
[X]Presenile dementia,Alzheimer's type	Eu00011
[X]Primary degen dementia, Alzheimer's type, presenile onset	Eu00012
[X]Alzheimer's disease type 2	Eu00013
[X]Dementia in Alzheimer's disease with late onset	Eu00100
[X]Alzheimer's disease type 1	Eu00111
[X]Senile dementia,Alzheimer's type	Eu00112
[X]Primary degen dementia of Alzheimer's type, senile onset	Eu00113
[X]Dementia in Alzheimer's dis, atypical or mixed type	Eu00200
[X]Dementia in Alzheimer's disease, unspecified	Eu00z00
[X]Alzheimer's dementia unspec	Eu00z11
[X]Vascular dementia	Eu01.00
[X]Arteriosclerotic dementia	Eu01.11
[X]Vascular dementia of acute onset	Eu01000
[X]Multi-infarct dementia	Eu01100
[X]Predominantly cortical dementia	Eu01111
[X]Subcortical vascular dementia	Eu01200
[X]Mixed cortical and subcortical vascular dementia	Eu01300

[X]Other vascular dementia	Eu01y00
[X]Vascular dementia, unspecified	Eu01z00
[X]Dementia in other diseases classified elsewhere	Eu02.00
[X]Dementia in Pick's disease	Eu02000
[X]Dementia in Creutzfeldt-Jakob disease	Eu02100
[X]Dementia in Huntington's disease	Eu02200
[X]Dementia in Parkinson's disease	Eu02300
[X]Dementia in human immunodef virus [HIV] disease	Eu02400
[X]Dementia in other specified diseases classif elsewhere	Eu02y00
[X] Unspecified dementia	Eu02z00
[X] Presenile dementia NOS	Eu02z11
[X] Primary degenerative dementia NOS	Eu02z13
[X] Senile dementia NOS	Eu02z14
[X] Senile dementia, depressed or paranoid type	Eu02z16
[X]Delirium superimposed on dementia	Eu04100

Table j-vi Codes for Chronic pulmonary disease

description	medcode
Recurrent wheezy bronchitis	H30..12
Chronic bronchitis	H31..00
Chronic asthmatic bronchitis	H312000
Chronic wheezy bronchitis	H312011
Emphysematous bronchitis	H312100
Acute exacerbation of chronic obstructive airways disease	H312200
Bronchiolitis obliterans	H312300
Obstructive chronic bronchitis NOS	H312z00
Emphysema	H32..00
Chronic bullous emphysema	H320.00
Segmental bullous emphysema	H320000
Zonal bullous emphysema	H320100
Giant bullous emphysema	H320200
Bullous emphysema with collapse	H320300
Chronic bullous emphysema NOS	H320z00
Panlobular emphysema	H321.00
Centrilobular emphysema	H322.00
Other emphysema	H32y.00
Atrophic (senile) emphysema	H32y100
MacLeod's unilateral emphysema	H32y200
Other emphysema NOS	H32yz00
Emphysema NOS	H32z.00
Asthma	H33..00
Bronchial asthma	H33..11
Bronchiectasis	H34..00
Extrinsic allergic alveolitis	H35..00
Other allergic alveolitis	H35y.00
Other allergic alveolitis NOS	H35yz00
Allergic alveolitis and pneumonitis NOS	H35z.00
Allergic extrinsic alveolitis NOS	H35z000
Allergic alveolitis and pneumonitis NOS	H35zz00
Mild chronic obstructive pulmonary disease	H36..00
Moderate chronic obstructive pulmonary disease	H37..00
Severe chronic obstructive pulmonary disease	H38..00
Other specified chronic obstructive airways disease	H3y..00
Other specified chronic obstructive pulmonary disease	H3y..11
Chronic obstructive airways disease NOS	H3z..00
Chronic obstructive pulmonary disease NOS	H3z..11
Chronic emphysema due to chemical fumes	H464000
Obliterative bronchiolitis due to chemical fumes	H464100
Chronic pulmonary fibrosis due to chemical fumes	H464200
Chronic respiratory conditions due to chemical fumes NOS	H464z00
Idiopathic fibrosing alveolitis	H563.00

Cryptogenic fibrosing alveolitis	H563.12
Idiopathic fibrosing alveolitis NOS	H563z00
Other lung disease NEC	H58y.00
Lung disease NOS	H58z.00
[X]Other emphysema	Hyu3000
[X]Other specified chronic obstructive pulmonary disease	Hyu3100

Table j-vii Codes for Connective tissue disease

description	medcode
Behcet's syndrome	AD61.00
Polyneuropathy in collagen vascular disease	F371.00
Polyneuropathy in disseminated lupus erythematosus	F371000
Polyneuropathy in polyarteritis nodosa	F371100
Polyneuropathy in collagen vascular disease NOS	F371z00
Muscular dystrophies and other myopathies	F39..00
Symptomatic inflammatory myopathy in disease EC	F396.00
Myopathy due to disseminated lupus erythematosus	F396100
Myopathy due to polyarteritis nodosa	F396300
Eyelid discoid lupus erythematosus	F4D3300
Arterial, arteriole and capillary disease	G7...00
Capillary disease	G7...11
Polyarteritis nodosa and allied conditions	G75..00
Polyarteritis nodosa	G750.00
Wegener's granulomatosis	G754.00
Juvenile polyarteritis	G759.00
Polyarteritis nodosa and allied conditions NOS	G75z.00
Lung disease with systemic lupus erythematosus	H57y400
Nephrotic syndrome in polyarteritis nodosa	K01x300
Lupus erythematosus	M154.00
Lupus erythematosus chronicus	M154000
Discoid lupus erythematosus	M154100
Lupus erythematosus migrans	M154200
Lupus erythematosus nodularis	M154300
Lupus erythematosus profundus	M154400
Lupus erythematosus tumidus	M154500
Lupus erythematosus unguium mutilans	M154600
Subacute cutaneous lupus erythematosus	M154700
Lupus erythematosus NOS	M154z00
[X]Other local lupus erythematosus	Myu7800
Musculoskeletal and connective tissue diseases	N....00
Connective tissue diseases	N....11
Arthropathies and related disorders	N0...00
Diffuse diseases of connective tissue	N00..00
Collagen diseases	N00..11
Systemic lupus erythematosus	N000.00
Disseminated lupus erythematosus	N000000
Drug-induced systemic lupus erythematosus	N000200
Systemic lupus erythematosus with organ or sys involv	N000300
Systemic lupus erythematosus with pericarditis	N000400
Systemic lupus erythematosus NOS	N000z00
Other specified diffuse collagen diseases	N00y.00
Collagen disease NOS	N00z.00

Arthropathy in Behcet's syndrome	N012.00
Arthropathy in Behcet's syndrome of unspecified site	N012000
Behcet's syndrome arthropathy	N012011
Arthropathy in Behcet's syndrome of the shoulder region	N012100
Arthropathy in Behcet's syndrome of the upper arm	N012200
Arthropathy in Behcet's syndrome of the forearm	N012300
Arthropathy in Behcet's syndrome of the hand	N012400
Arthropathy in Behcet's syndrome of the pelvis/thigh	N012500
Arthropathy in Behcet's syndrome of the lower leg	N012600
Arthropathy in Behcet's syndrome of the ankle and foot	N012700
Arthropathy in Behcet's syndrome of multiple sites	N012x00
Arthropathy in Behcet's syndrome of other specified sites	N012y00
Arthropathy in Behcet's syndrome NOS	N012z00
Rheumatism, excluding the back	N2...00
Polymyalgia rheumatica	N20..00
Polymyalgia	N20..11
Giant cell arteritis with polymyalgia rheumatica	N200.00
Scoliosis in connective tissue anomalies	N374D00
Musculoskeletal or connective tissue diseases OS	Ny...00
[X]Addtnl musculskeletal+connectv tissue dis classfctn terms	Nyu..00
[X]Systemic connective tissue disorders	Nyu4.00
[X]Other conditions related to polyarteritis nodosa	Nyu4000
[X]Other forms of systemic lupus erythematosus	Nyu4300
[X]Other systemic diseases of connective tissue	Nyu4700
[X]Systemic disorders/connective tissue in other diseases CE	Nyu4C00
[X]Other disord musculoskeletal system and connective tissue	NyuE.00
Musculoskeletal and connective tissue diseases NOS	Nz...00
Unspecified anomaly of connective tissue	PGz4.00

Table j-viii Codes for Ulcer disease

description	medcode
Peptic ulcer symptoms	1956
Oesophageal, stomach and duodenal diseases	J1...00
Duodenal diseases	J1...11
Ulcerative oesophagitis	J101600
Ulcer of oesophagus	J102.00
Peptic ulcer of oesophagus	J102000
Oesophageal ulcer due to aspirin	J102200
Oesophageal ulcer due to chemicals	J102300
Oesophageal ulcer due to medicines	J102400
Barrett's ulcer of oesophagus	J102500
Ulcer of oesophagus NOS	J102z00
Gastric ulcer - (GU)	J11..00
Prepyloric ulcer	J11..11
Pyloric ulcer	J11..12
Acute gastric ulcer	J110.00
Acute gastric ulcer without mention of complication	J110000
Acute gastric ulcer with haemorrhage	J110100
Bleeding acute gastric ulcer	J110111
Acute gastric ulcer with perforation	J110200
Acute gastric ulcer with haemorrhage and perforation	J110300
Acute gastric ulcer with obstruction	J110400
Acute gastric ulcer unspecified	J110y00
Acute gastric ulcer NOS	J110z00
Chronic gastric ulcer	J111.00
Chronic gastric ulcer without mention of complication	J111000
Chronic gastric ulcer with haemorrhage	J111100
Bleeding chronic gastric ulcer	J111111
Chronic gastric ulcer with perforation	J111200
Perforated chronic gastric ulcer	J111211
Chronic gastric ulcer with haemorrhage and perforation	J111300
Chronic gastric ulcer with obstruction	J111400
Chronic gastric ulcer unspecified	J111y00
Chronic gastric ulcer NOS	J111z00
Unspecified gastric ulcer	J11y.00
Unspecified gastric ulcer without mention of complication	J11y000
Unspecified gastric ulcer with haemorrhage	J11y100
Unspecified gastric ulcer with perforation	J11y200
Unspecified gastric ulcer with haemorrhage and perforation	J11y300
Unspecified gastric ulcer with obstruction	J11y400
Unspec gastric ulcer; unspec haemorrhage and/or perforation	J11yy00
Unspecified gastric ulcer NOS	J11yz00
Gastric ulcer NOS	J11z.00
Multiple gastric ulcers	J11z.12

Duodenal ulcer - (DU)	J12..00
Acute duodenal ulcer	J120.00
Acute duodenal ulcer without mention of complication	J120000
Acute duodenal ulcer with haemorrhage	J120100
Acute duodenal ulcer with perforation	J120200
Acute duodenal ulcer with haemorrhage and perforation	J120300
Acute duodenal ulcer with obstruction	J120400
Acute duodenal ulcer unspecified	J120y00
Acute duodenal ulcer NOS	J120z00
Chronic duodenal ulcer	J121.00
Chronic duodenal ulcer without mention of complication	J121000
Chronic duodenal ulcer with haemorrhage	J121100
Bleeding chronic duodenal ulcer	J121111
Chronic duodenal ulcer with perforation	J121200
Perforated chronic duodenal ulcer	J121211
Chronic duodenal ulcer with haemorrhage and perforation	J121300
Chronic duodenal ulcer with obstruction	J121400
Chronic duodenal ulcer unspecified	J121y00
Chronic duodenal ulcer NOS	J121z00
Duodenal ulcer disease	J122.00
Recurrent duodenal ulcer	J124.00
Unspecified duodenal ulcer	J12y.00
Unspecified duodenal ulcer without mention of complication	J12y000
Unspecified duodenal ulcer with haemorrhage	J12y100
Unspecified duodenal ulcer with perforation	J12y200
Unspecified duodenal ulcer with haemorrhage and perforation	J12y300
Unspecified duodenal ulcer with obstruction	J12y400
Unspec duodenal ulcer; unspec haemorrhage and/or perforation	J12yy00
Unspecified duodenal ulcer NOS	J12yz00
Duodenal ulcer NOS	J12z.00
Peptic ulcer - (PU) site unspecified	J13..00
Stress ulcer NOS	J13..11
Acute peptic ulcer	J130.00
Acute peptic ulcer without mention of complication	J130000
Acute peptic ulcer with haemorrhage	J130100
Acute peptic ulcer with perforation	J130200
Acute peptic ulcer with haemorrhage and perforation	J130300
Acute peptic ulcer with obstruction	J130400
Acute peptic ulcer unspecified	J130y00
Acute peptic ulcer NOS	J130z00
Chronic peptic ulcer	J131.00
Chronic peptic ulcer without mention of complication	J131000
Chronic peptic ulcer with haemorrhage	J131100
Chronic peptic ulcer with perforation	J131200
Chronic peptic ulcer with haemorrhage and perforation	J131300
Chronic peptic ulcer with obstruction	J131400

Chronic peptic ulcer unspecified	J131y00
Chronic peptic ulcer NOS	J131z00
Unspecified peptic ulcer	J13y.00
Unspecified peptic ulcer without mention of complication	J13y000
Unspecified peptic ulcer with haemorrhage	J13y100
Unspecified peptic ulcer with perforation	J13y200
Unspecified peptic ulcer with haemorrhage and perforation	J13y300
Unspecified peptic ulcer with obstruction	J13y400
Unspec peptic ulcer; unspec haemorrhage and/or perforation	J13yy00
Unspecified peptic ulcer NOS	J13yz00
Peptic ulcer NOS	J13z.00
Gastrojejunal ulcer (GJU)	J14..00
Gastrocolic ulcer	J14..12
Jejunal ulcer	J14..13
Marginal ulcer	J14..14
Stomal ulcer	J14..15
Acute gastrojejunal ulcer	J140.00
Acute gastrojejunal ulcer without mention of complication	J140000
Acute gastrojejunal ulcer with haemorrhage	J140100
Acute gastrojejunal ulcer with perforation	J140200
Acute gastrojejunal ulcer with haemorrhage and perforation	J140300
Acute gastrojejunal ulcer with obstruction	J140400
Acute gastrojejunal ulcer unspecified	J140y00
Acute gastrojejunal ulcer NOS	J140z00
Chronic gastrojejunal ulcer	J141.00
Chronic gastrojejunal ulcer without mention of complication	J141000
Chronic gastrojejunal ulcer with haemorrhage	J141100
Chronic gastrojejunal ulcer with perforation	J141200
Chronic gastrojejunal ulcer with haemorrhage and perforation	J141300
Chronic gastrojejunal ulcer with obstruction	J141400
Chronic gastrojejunal ulcer unspecified	J141y00
Chronic gastrojejunal ulcer NOS	J141z00
Unspecified gastrojejunal ulcer	J14y.00
Unspecified gastrojejunal ulcer without mention complication	J14y000
Unspecified gastrojejunal ulcer with haemorrhage	J14y100
Unspecified gastrojejunal ulcer with perforation	J14y200
Unspec gastrojejunal ulcer with haemorrhage and perforation	J14y300
Unspecified gastrojejunal ulcer with obstruction	J14y400
Unspec gastrojejunal ulcer; unspec haemorrhage/perforation	J14yy00
Unspecified gastrojejunal ulcer NOS	J14yz00
Gastrojejunal ulcer NOS	J14z.00
Other stomach and duodenal disorders	J17..00
Other stomach and duodenal disorders	J17y.00
Primary ulcer of intestine	J57y800
Ulceration of colon	J57y900
Ulceration of intestine NOS	J57yA00

Table j-ix Codes for Diabetes (not specifying end organ damage)

description	medcode
Initial diabetic assessment	66A1.00
Follow-up diabetic assessment	66A2.00
Diabetic on diet only	66A3.00
Diabetic on oral treatment	66A4.00
Diabetic on insulin	66A5.00
Has seen dietician - diabetes	66A8.00
Unstable diabetes	66AJ.11
Diabetic - poor control NOS	66AJz00
Diabetes: practice programme	66AP.00
Diabetes: shared care programme	66AQ.00
Diabetes care by hospital only	66AU.00
Diabetic on insulin and oral treatment	66AV.00
Diabetic monitoring NOS	66AZ.00
Under care of diabetologist	9NN8.00
Under care of diabetes specialist nurse	9NN9.00
Diabetes mellitus	C10..00
Diabetes mellitus with no mention of complication	C100.00
Diabetes mellitus, juvenile type, no mention of complication	C100000
Insulin dependent diabetes mellitus	C100011
Diabetes mellitus, adult onset, no mention of complication	C100100
Maturity onset diabetes	C100111
Non-insulin dependent diabetes mellitus	C100112
Diabetes mellitus NOS with no mention of complication	C100z00
Insulin dependent diabetes mellitus	C108.00
IDDM-Insulin dependent diabetes mellitus	C108.11
Type 1 diabetes mellitus	C108.12
Type I diabetes mellitus	C108.13
Unstable insulin dependent diabetes mellitus	C108400
Unstable type I diabetes mellitus	C108411
Unstable type 1 diabetes mellitus	C108412
Insulin dependent diabetes mellitus - poor control	C108800
Type I diabetes mellitus - poor control	C108811
Type 1 diabetes mellitus - poor control	C108812
Insulin dependent diabetes maturity onset	C108900
Type I diabetes mellitus maturity onset	C108911
Type 1 diabetes mellitus maturity onset	C108912
Insulin-dependent diabetes without complication	C108A00
Type I diabetes mellitus without complication	C108A11
Type 1 diabetes mellitus without complication	C108A12
Non-insulin dependent diabetes mellitus	C109.00
NIDDM - Non-insulin dependent diabetes mellitus	C109.11
Type 2 diabetes mellitus	C109.12

Type II diabetes mellitus	C109.13
Non-insulin dependent diabetes mellitus - poor control	C109700
Type II diabetes mellitus - poor control	C109711
Type 2 diabetes mellitus - poor control	C109712
Reaven's syndrome	C109800
Non-insulin-dependent diabetes mellitus without complication	C109900
Type II diabetes mellitus without complication	C109911
Type 2 diabetes mellitus without complication	C109912
Insulin treated Type 2 diabetes mellitus	C109J00
Insulin treated non-insulin dependent diabetes mellitus	C109J11
Insulin treated Type II diabetes mellitus	C109J12
Malnutrition-related diabetes mellitus	C10A.00
Diabetes mellitus induced by steroids	C10B.00
Steroid induced diabetes mellitus without complication	C10B000
Diabetes mellitus autosomal dominant	C10C.00
Maturity onset diabetes in youth	C10C.11
Maturity onset diabetes in youth type 1	C10C.12
Diabetes mellitus autosomal dominant type 2	C10D.00
Maturity onset diabetes in youth type 2	C10D.11
Type 1 diabetes mellitus	C10E.00
Type I diabetes mellitus	C10E.11
Insulin dependent diabetes mellitus	C10E.12
Unstable type 1 diabetes mellitus	C10E400
Unstable type I diabetes mellitus	C10E411
Unstable insulin dependent diabetes mellitus	C10E412
Type 1 diabetes mellitus - poor control	C10E800
Type I diabetes mellitus - poor control	C10E811
Insulin dependent diabetes mellitus - poor control	C10E812
Type 1 diabetes mellitus maturity onset	C10E900
Type I diabetes mellitus maturity onset	C10E911
Insulin dependent diabetes maturity onset	C10E912
Type 1 diabetes mellitus without complication	C10EA00
Type I diabetes mellitus without complication	C10EA11
Insulin-dependent diabetes without complication	C10EA12
Type 2 diabetes mellitus	C10F.00
Type II diabetes mellitus	C10F.11
Type 2 diabetes mellitus - poor control	C10F700
Type II diabetes mellitus - poor control	C10F711
Reaven's syndrome	C10F800
Metabolic syndrome X	C10F811
Type 2 diabetes mellitus without complication	C10F900
Type II diabetes mellitus without complication	C10F911
Secondary pancreatic diabetes mellitus	C10G.00
Secondary pancreatic diabetes mellitus without complication	C10G000
Diabetes mellitus induced by non-steroid drugs	C10H.00
Insulin autoimmune syndrome	C10J.00

Type A insulin resistance	C10K.00
Fibrocalculous pancreatopathy	C10L.00
Lipoatrophic diabetes mellitus	C10M.00
Lipoatrophic diabetes mellitus without complication	C10M000
Secondary diabetes mellitus	C10N.00
Secondary diabetes mellitus without complication	C10N000
Diabetes mellitus with other specified manifestation	C10y.00
Diabetes mellitus, juvenile, + other specified manifestation	C10y000
Diabetes mellitus, adult, + other specified manifestation	C10y100
Steroid induced diabetes	C11y000
[X]Diabetes mellitus	Cyu2.00
[X]Other specified diabetes mellitus	Cyu2000
Diabetes mellitus during pregnancy/childbirth/puerperium	L180.00
Diabetes mellitus - unspec whether in pregnancy/puerperium	L180000
Diabetes mellitus during pregnancy - baby delivered	L180100
Diabetes mellitus in puerperium - baby delivered	L180200
Diabetes mellitus during pregnancy - baby not yet delivered	L180300
Diabetes mellitus in pueperium - baby previously delivered	L180400
Pre-existing diabetes mellitus, insulin-dependent	L180500
Pre-existing diabetes mellitus, non-insulin-dependent	L180600
Pre-existing malnutrition-related diabetes mellitus	L180700
Diabetes mellitus arising in pregnancy	L180800
Gestational diabetes mellitus	L180811
Gestational diabetes mellitus	L180900
Pre-existing diabetes mellitus, unspecified	L180X00
Diabetes mellitus in pregnancy/childbirth/puerperium NOS	L180z00
Abnormal glucose tolerance test in pregnancy/childb/puerp	L188.00
GTT - glucose tolerance test abnormal in preg/childb/puerp	L188.11
[X]Pre-existing diabetes mellitus, unspecified	Lyu2900
[D]Drug induced hyperglycaemia	R10C.00
[D]Elevated blood glucose level	R10D.00
[D]Impaired glucose tolerance	R10E.00
Dietary advice for type I diabetes	ZC2C900
Diet advice for insulin-dependent diabetes	ZC2C911
Dietary advice for type II diabetes	ZC2CA00
Dietary advice non-insulin-dependent diabetes	ZC2CA11
Dietary advice for gestational diabetes	ZC2CB00
Referral to diabetes nurse	ZL62500
Referral to diabetic liaison nurse	ZL62600
[V]Dietary counselling in diabetes mellitus	ZV65312

Table j-x Codes for Hemiplegia

description	medcode
O/E - hemiplegia	2833
Hemiplegia	F22..00
Flaccid hemiplegia	F220.00
Spastic hemiplegia	F221.00
Left hemiplegia	F222.00
Right hemiplegia	F223.00
Hemiplegia NOS	F22z.00
Paraplegia - congenital	F230.11
Congenital hemiplegia	F231.00
Infantile hemiplegia NOS	F234.00

Table j-xi Codes for Moderate or severe renal disease

description	medcode
Renal colic	1A52.00
Renal colic, symptom	1A52.11
Ureteric colic	1A54.00
Dysuria	1A55.00
Strangury	1A56.00
O/E - kidney palpated	262..00
O/E - renal palpation	262..11
O/E - left kidney palpable	2622
O/E - right kidney palpable	2623
O/E - renal angle tenderness	2624
O/E - kidney palpable NOS	262Z.00
O/E - bladder palpated	263..00
O/E - bladder palpable	263..11
O/E: renal calculus	4G4..00
O/E: kidney stone	4G4..11
O/E: oxalate renal calculus	4G41.00
Phosphate kidney stone	4G42.11
O/E: uric acid renal calculus	4G43.00
O/E: cystine renal calculus	4G44.00
O/E: renal stone NOS	4G4Z.00
O/E - ureteric calculus	4G6..00
O/E - urethral calculus	4G7..00
O/E - bladder calculus	4G8..00
Dialysis for renal failure	7L1A.11
Renal dialysis	7L1A000
Thomas intravascular shunt for dialysis	7L1A011
Peritoneal dialysis	7L1A100
Haemodialysis NEC	7L1A200
Other specified compensation for renal failure	7L1Ay00
Compensation for renal failure NOS	7L1Az00
Placement ambulatory apparatus compensation renal failure	7L1B.00
Placement ambulatory dialysis apparatus - compens renal fail	7L1B.11
Insertion of ambulatory peritoneal dialysis catheter	7L1B000
Placement ambulatory apparatus- compensate renal failure OS	7L1By00
Placement ambulatory apparatus- compensate renal failure NOS	7L1Bz00
Placement other apparatus for compensation for renal failure	7L1C.00
Insertion of temporary peritoneal dialysis catheter	7L1C000
Placement other apparatus- compensate for renal failure OS	7L1Cy00
Placement other apparatus- compensate for renal failure NOS	7L1Cz00
Tuberculosis of kidney	A160.00
Renal tuberculosis	A160.11
Tuberculosis of bladder	A161.00
Tuberculosis of ureter	A162.00

Tuberculosis of other urinary organs	A163.00
Tuberculosis of urinary tract	A168.00
Syphilis of kidney	A954.00
Renal syphilis	A954.11
Hypertensive renal disease	G22..00
Nephrosclerosis	G22..11
Malignant hypertensive renal disease	G220.00
Benign hypertensive renal disease	G221.00
Hypertensive renal disease with renal failure	G222.00
Hypertensive renal disease NOS	G22z.00
Renal hypertension	G22z.11
Hypertensive heart and renal disease	G23..00
Malignant hypertensive heart and renal disease	G230.00
Benign hypertensive heart and renal disease	G231.00
Hypertensive heart&renal dis wth (congestive) heart failure	G232.00
Hypertensive heart and renal disease with renal failure	G233.00
Hyperten heart&renal dis+both(congestv)heart and renal fail	G234.00
Hypertensive heart and renal disease NOS	G23z.00
Aneurysm of renal artery	G721.00
Hyperplasia of renal artery	G763.00
Embolism and thrombosis of the renal vein	G823.00
Acute glomerulonephritis	K00..00
Acute nephritis	K00..11
Bright's disease	K00..12
Nephrotic syndrome	K01..00
Chronic glomerulonephritis	K02..00
Nephritis - chronic	K02..11
Nephropathy - chronic	K02..12
Nephritis and nephropathy unspecified	K03..00
Nephritis and nephropathy unspecified	K03..11
Nephropathy, unspecified	K03..12
Proliferative nephritis unspecified	K030.00
Membranous nephritis unspecified	K031.00
Membranoproliferative nephritis unspecified	K032.00
Rapidly progressive nephritis unspecified	K033.00
Renal cortical necrosis unspecified	K034.00
Renal medullary necrosis unspecified	K035.00
Tubulo-interstit nephritis, not specif as acute or chron	K03T.00
Unspecif nephr synd, diff concentric glomerulonephritis	K03U.00
Unspecified nephritic syndrome, dense deposit disease	K03V.00
Unsp nephrit synd, diff endocap prolif glomerulonephritis	K03W.00
Unsp nephrit synd, diff mesang prolif glomerulonephritis	K03X.00
Other nephritis and nephrosis unspecified	K03y.00
Unspecified glomerulonephritis NOS	K03z.00
Acute renal failure	K04..00
Acute renal tubular necrosis	K040.00

Acute renal cortical necrosis	K041.00
Acute renal medullary necrosis	K042.00
Necrotising renal papillitis	K042.11
Acute drug-induced renal failure	K043.00
Other acute renal failure	K04y.00
Acute renal failure NOS	K04z.00
Chronic renal failure	K05..00
Chronic uraemia	K05..11
End stage renal failure	K05..12
End stage renal failure	K050.00
Renal failure unspecified	K06..00
Uraemia NOS	K06..11
Renal impairment	K060.00
Impaired renal function	K060.11
Renal sclerosis unspecified	K07..00
Atrophy of kidney	K070.00
Renal fibrosis	K071.00
Glomerulosclerosis	K072.00
Renal sclerosis NOS	K07z.00
Impaired renal function disorder	K08..00
Renal osteodystrophy	K080.00
Phosphate-losing tubular disorders	K080000
Renal osteodystrophy NOS	K080z00
Nephrogenic diabetes insipidus	K081.00
Other impaired renal function disorder	K08y.00
Hypokalaemic nephropathy	K08y000
Lightwood - Albright syndrome	K08y200
Albright's renal tubular acidosis	K08y211
Renal function impairment with growth failure	K08y300
Renal tubular acidosis	K08y400
Renal tubular acidaemia	K08y412
Acute interstitial nephritis	K08y500
Other impaired renal function disorder NOS	K08yz00
Renal acidaemia	K08yz11
Renotubular acidaemia	K08yz12
Impaired renal function disorder NOS	K08z.00
Small kidney of unknown cause	K09..00
Glomerular disease	K0A..00
Renal tubulo-interstitial disorders in diseases EC	K0B..00
Ren tubulo-interstital disord infect and parasitic dis EC	K0B0.00
Renal tubulo-interstitial disorder/ neoplastic diseases	K0B1.00
Ren tub-interst disordr/blood dis+disordr inv immune mech	K0B2.00
Renal tubulo-interstitial disorders in metabolic diseases	K0B3.00
Ren tub-interstitl disordr/systemc connectv tiss disorder	K0B4.00
Renal tubulo-interstitial disorder in SLE	K0B4000
Renal tubulo-interstitial disordrs in transplant rejectn	K0B5.00

Balkan nephropathy	K0B6.00
Drug/heavy-metal-induced tubulo-interstitial and tub conditn	K0C..00
End-stage renal disease	K0D..00
Other specified nephritis, nephrosis or nephrotic syndrome	K0y..00
Nephritis, nephrosis and nephrotic syndrome NOS	K0z..00
Infections of kidney	K10..00
Renal infections	K10..11
Chronic pyelonephritis	K100.00
Acute pyelonephritis	K101.00
Renal and perinephric abscess	K102.00
Renal abscess	K102000
Perinephric abscess	K102100
Renal carbuncle	K102200
Renal and perinephric abscess NOS	K102z00
Pyeloureteritis cystica	K103.00
Ureteritis cystica	K103.11
Infestation of renal pelvis with ureter	K103.12
Xanthogranulomatous pyelonephritis	K104.00
Pyelonephritis and pyonephrosis unspecified	K10y.00
Infection of kidney NOS	K10z.00
Hydronephrosis	K11..00
Hydrocalycosis	K110.00
Hydroureteronephrosis	K111.00
Hydronephrosis with renal and ureteral calculous obstruction	K112.00
Hydronephrosis with ureteropelvic junction obstruction	K113.00
Hydronephrosis with pelviureteric junction obstruction	K113.11
Hydronephrosis with ureteral stricture NEC	K11X.00
Hydronephrosis NOS	K11z.00
Calculus of kidney and ureter	K12..00
Kidney calculus	K12..11
Urinary calculus	K12..12
Calculus of kidney	K120.00
Nephrolithiasis NOS	K120.11
Renal calculus	K120.12
Renal stone	K120.13
Staghorn calculus	K120000
Renal calculus NOS	K120z00
Calculus of ureter	K121.00
Ureteric calculus	K121.11
Ureteric stone	K121.12
Ureterolithiasis	K121.13
Calculus of kidney with calculus of ureter	K122.00
Urinary calculus NOS	K12z.00
Other kidney and ureter disorders	K13..00
Other kidney disorders	K13..11
Other ureter disorders	K13..12

Nephroptosis	K130.00
Floating kidney	K130.11
Mobile kidney	K130.12
Hypertrophy of kidney	K131.00
Acquired cyst of kidney	K132.00
Stricture of ureter	K133.00
Other ureteric obstruction	K134.00
Hydroureter	K135.00
Benign postural proteinuria	K136.00
Orthostatic proteinuria	K136.11
Vesicoureteric reflux	K137.00
Ureteric reflux	K137.11
Vascular disorders of kidney	K138.00
Renal vascular disorders	K138.11
Renal artery embolism	K138000
Renal artery embolus	K138011
Renal artery haemorrhage	K138100
Renal artery thrombosis	K138200
Intrarenal haematoma	K138300
Renal vascular disorders NOS	K138z00
Renal infarction	K138z11
Other kidney and ureteric disorders	K13y.00
Ureteric fistula	K13y000
Adhesions of kidney	K13y100
Adhesions of ureter	K13y200
Periureteritis	K13y300
Pyelectasia	K13y400
Polyp of ureter	K13y500
Ureterocele - acquired	K13y600
Idiopathic dilation of ureter	K13y611
Megaloureter - acquired	K13y700
Perirenal haematoma	K13y800
Ureteric neuromuscular incoordination	K13y900
Other kidney and ureteric disorders NOS	K13yz00
Salt-losing nephritis	K13yz11
Kidney and ureter disease NOS	K13z.00
Lower urinary tract calculus	K14..00
Cystitis	K15..00
Other disorders of bladder	K16..00
Urethritis due to non venereal causes	K17..00
Periurethritis	K17..11
Urethral stricture	K18..00
Pinhole meatus	K18..11
Other urethral and urinary tract disorders	K19..00
Other urethral disorders	K19..11
Urinary calculus in schistosomiasis	K1A..00

Other specified diseases of urinary system	K1y..00
Other urinary system diseases NOS	K1z..00
[X]Glomerular diseases	Kyu0.00
[X]Renal tubulo-interstitial diseases	Kyu1.00
[X]Other chronic tubulo-interstitial nephritis	Kyu1000
[X]Other and unspecified hydronephrosis	Kyu1100
[X]Other obstructive and reflux uropathy	Kyu1200
[X]Obstructive and reflux uropathy, unspecified	Kyu1300
[X]Nephropathy induced by other drugs+biological substances	Kyu1400
[X]Toxic nephropathy, not elsewhere classified	Kyu1500
[X]Other specified renal tubulo-interstitial diseases	Kyu1600
[X]Renal tubulo-interstitial disordr/infect+parasitic dis CE	Kyu1700
[X]Renal tubulo-interstitial disordrs/neoplastic diseases CE	Kyu1800
[X]Renal tub-interstl disord/bld dis+disord invl imm mech CE	Kyu1900
[X]Renal tubulo-interstitial disorders/metabolic diseases CE	Kyu1A00
[X]Renal tubul-interstitl disordrs/connectv tissu disordr CE	Kyu1B00
[X]Renal tubulo-interstitial disorders/transplant rejection	Kyu1C00
[X]Renal tubulo-interstitial disorders in other diseases CE	Kyu1D00
[X]Tubulo-interstit nephritis, not specif as acute or chron	Kyu1E00
[X]Hydronephrosis with ureteral stricture NEC	Kyu1F00
[X]Renal failure	Kyu2.00
[X]Other acute renal failure	Kyu2000
[X]Other chronic renal failure	Kyu2100
[X]Urolithiasis	Kyu3.00
[X]Other disorders of kidney and ureter	Kyu4.00
[X]Other disorders resulting/impaired renal tubular function	Kyu4000
[X]Other specified disorders of kidney and ureter	Kyu4100
[X]Oth disordrs/kidney+ureter/infects+parasitic diseases CE	Kyu4200
[X]Other disorders of kidney+ureter in other diseases CE	Kyu4300
[X]Other diseases of urinary system	Kyu5.00
[X]Other disorders of genitourinary tract	KyuA.00
Incomplete spontaneous abortion with renal failure	L041300
Complete spontaneous abortion with renal failure	L042300
Unspecified legal abortion with renal failure	L050300
Incomplete legal abortion with renal failure	L051300
Complete legal abortion with renal failure	L052300
Unspecified illegal abortion with renal failure	L060300
Incomplete illegal abortion with renal failure	L061300
Complete illegal abortion with renal failure	L062300
Unspecified abortion with renal failure	L070300
Unspecified abortion with metabolic disorder	L070400
Unspecified abortion with shock	L070500
Unspecified abortion with embolism	L070600
Unspecified abortion with other specified complication	L070w00
Unspecified abortion with complication NOS	L070x00
Unspecified abortion with no mention of complication	L070y00

Unspecified abortion NOS	L070z00
Unspecified incomplete abortion +genital tract/pelvic infect	L071000
Unspecified incomplete abortion + delayed/excess haemorrhage	L071100
Unspecified complete abortion with renal failure	L072300
Failed attempted abortion with renal failure	L083.00
Renal failure following abortive pregnancy	L093.00
Oliguria following abortive pregnancy	L093000
Acute renal failure following abortive pregnancy	L093100
Renal shutdown following abortive pregnancy	L093200
Renal tubular necrosis following abortive pregnancy	L093300
Uraemia following abortive pregnancy	L093400
Renal failure NOS following abortive pregnancy	L093z00
Renal hypertension in pregnancy/childbirth/puerperium	L121.00
Renal hypertension in pregnancy/childbirth/puerp unspecified	L121000
Renal hypertension in pregnancy/childbirth/puerp - delivered	L121100
Renal hypertension in preg/childb/puerp -deliv with p/n comp	L121200
Renal hypertension in preg/childbirth/puerp - not delivered	L121300
Renal hypertension in preg/childb/puerp + p/n complication	L121400
Renal hypertension in pregnancy/childbirth/puerperium NOS	L121z00
Other pre-existing hypertension in preg/childbirth/puerp	L122.00
Pre-exist hyperten heart renal dis comp preg chldbirth/puerp	L128100
Unspecified renal disease in pregnancy	L162.00
Unspecified renal disease in pregnancy unspecified	L162000
Unspecified renal disease in pregnancy - delivered	L162100
Unspecified renal disease in pregnancy - del with p/n comp	L162200
Unspecified renal disease in pregnancy - not delivered	L162300
Unspecified renal disease in pregnancy with p/n complication	L162400
Unspecified renal disease in pregnancy NOS	L162z00
Acute renal failure following labour and delivery	L393.00
Post-delivery acute renal failure unspecified	L393000
Post-delivery acute renal failure - delivered with p/n prob	L393100
Post-delivery acute renal failure with postnatal problem	L393200
Post-delivery acute renal failure NOS	L393z00
Renal agenesis and dysgenesis	PD0..00
Renal agenesis, unspecified	PD00.00
Bilateral renal agenesis	PD00000
Unilateral renal agenesis	PD00100
Renal agenesis, unspecified NOS	PD00z00
Congenital renal atrophy	PD01.00
Congenital absence of kidney	PD02.00
Hypoplasia of kidney	PD03.00
Bilateral renal hypoplasia	PD03000
Potter's syndrome	PD03011
Unilateral renal hypoplasia	PD03100
Dysplasia of kidney	PD04.00
Bilateral renal dysplasia	PD04000

Bilateral renal dysgenesis	PD04011
Unilateral renal dysplasia	PD04100
Unilateral renal dysgenesis	PD04111
Dysplasia of kidney NOS	PD04z00
Renal agenesis or dysgenesis NOS	PD0z.00
Congenital cystic kidney disease	PD1..00
Congenital cystic renal disease	PD1..11
Fibrocystic kidney	PD1..12
Polycystic kidney	PD1..13
Sponge kidney	PD1..14
Congenital renal cyst, single	PD10.00
Polycystic kidney disease	PD11.00
Medullary cystic disease	PD12.00
Multicystic renal dysplasia	PD13.00
Multicystic kidney	PD13.11
Other specified congenital cystic kidney disease	PD1y.00
Fibrocystic kidney disease	PD1y000
Fibrocystic renal degeneration	PD1y011
Other congenital cystic kidney disease NOS	PD1yz00
Congenital cystic kidney disease NOS	PD1z.00
Renal pelvis and ureter obstructive defects	PD2..00
Atresia of ureter	PD20.00
Occlusion of ureter	PD21.00
Congenital ureteric valves	PD21.11
Congenital stricture of ureter	PD22.00
Congenital stenosis of ureter	PD22.11
Congenital hydronephrosis	PD23.00
Congenital dilated renal pelvis	PD23.11
Congenital dilatation of ureter	PD24.00
Hydroureter - congenital	PD25.00
Megaloureter - congenital	PD26.00
Ureterocele - congenital	PD27.00
Impervious ureter	PD28.00
Other specified obstructive defect of renal pelvis or ureter	PD2y.00
Obstructive defect of renal pelvis or ureter NOS	PD2z.00
Other specified renal anomaly	PD3..00
Accessory kidney	PD30.00
Duplication of kidney	PD30.11
Renal duplication NEC	PD30.12
Supernumerary kidney	PD30.13
Congenital calculus of kidney	PD31.00
Congenital displaced kidney	PD32.00
Discoid kidney	PD33.00
Double kidney with double pelvis	PD34.00
Duplex kidneys	PD34.11
Pyelon duplex	PD34.12

Ectopic kidney	PD35.00
Pelvic kidney	PD35.11
Fusion of kidneys	PD36.00
Giant kidney	PD37.00
Horseshoe kidney	PD38.00
Hyperplasia of kidney	PD39.00
Lobulation of kidney	PD3A.00
Ren arcuatus	PD3A.11
Ren unguliformis	PD3A.12
Malrotation of kidney	PD3B.00
Triple kidney with triple pelvis	PD3C.00
Trifid kidney	PD3C.11
Pyelon triplex	PD3C.12
Enlarged kidney	PD3D.00
Other specified renal anomaly NOS	PD3z.00
Other specified ureter anomalies	PD4..00
Absent ureter	PD40.00
Accessory ureter	PD41.00
Deviation of ureter	PD42.00
Displaced ureteric orifice	PD43.00
Double ureter	PD44.00
Duplication of ureter	PD44.11
Ectopic ureter	PD45.00
Congenital displacement of opening of ureter	PD45.11
Ectopic insertion of ureter	PD45.12
Anomalous ureter implantation	PD46.00
Congenital vesico-uretero-renal reflux	PD47.00
Other specified ureter anomaly NOS	PD4z.00
Exstrophy of urinary bladder	PD5..00
Ectopia vesicae	PD5..11
Ectopic bladder	PD5..12
Urethra and bladder neck atresia and stenosis	PD6..00
Other specified bladder and urethral anomalies	PDy..00
Urinary system anomalies NOS	PDz..00
[D]Renal colic	R080.00
[D]Renal colic, unspecified	R080000
[D]Ureteric colic	R080100
[D]Renal colic NOS	R080z00
[D]Dysuria	R081.00
[D]Retention of urine	R082.00
[D]Incontinence of urine	R083.00
[D]Micturition frequency and polyuria	R084.00
[D]Oliguria and anuria	R085.00
[D]Other urination abnormality	R086.00
[D]Difficulty with micturition	R086.11
[D]Urethral discharge	R087.00

[D]Extravasation of urine	R088.00
[D]Other urinary system symptom	R08z.00
[D]Urinary system symptoms NOS	R08zz00
[D]Bladder filling defect	R135000
[D]Kidney filling defect	R135100
[D]Ureter filling defect	R135200
[D]Renal scarring	R135300
[D]Genitourinary x-ray or scan abnormality NOS	R135z00
[D]Renal function test abnormal	R144.00
[D]Kidney function test abnormal	R144.11
Kidney injury without open wound into cavity, unspecified	S760000
Kidney haematoma without mention of open wound into cavity	S760100
Renal haematoma without mention of open wound into cavity	S760111
Kidney laceration without mention of open wound into cavity	S760200
Kidney parenchyma disruption without open wound to cavity	S760300
Kidney injury without mention of open wound into cavity NOS	S760z00
Kidney injury with open wound into cavity, unspecified	S761000
Kidney haematoma with open wound into cavity	S761100
Renal haematoma with open wound into cavity	S761111
Kidney laceration with open wound into cavity	S761200
Kidney parenchyma disruption with open wound into cavity	S761300
Kidney injury with open wound into cavity NOS	S761z00
Renal failure following crush syndrome	SK05.00
Renal failure after crushing	SK05.11
Traumatic anuria - crush syndrome	SK05.12
Oliguria as a complication of care	SP15200
Anuria as a complication of care	SP15300
Renal failure as a complication of care	SP15400
Kidney failure as a complication of care	SP15411
Post operative renal failure	SP15412
Uraemia - post operative	SP15413
Kidney transplant with complication, without blame	TB00100
Renal transplant with complication, without blame	TB00111
Kidney dialysis with complication, without blame	TB11.00
Renal dialysis with complication, without blame	TB11.11

Table j-xii Codes for Diabetes with end organ damage

description	medcode
Retinal abnormality - diabetes related	2BBF.00
O/E - diabetic maculopathy present both eyes	2BBL.00
O/E - diabetic maculopathy absent both eyes	2BBM.00
O/E - right eye background diabetic retinopathy	2BBP.00
O/E - left eye background diabetic retinopathy	2BBQ.00
O/E - right eye preproliferative diabetic retinopathy	2BBR.00
O/E - left eye preproliferative diabetic retinopathy	2BBS.00
O/E - right eye proliferative diabetic retinopathy	2BBT.00
O/E - left eye proliferative diabetic retinopathy	2BBV.00
O/E - right eye diabetic maculopathy	2BBW.00
O/E - left eye diabetic maculopathy	2BBX.00
O/E - sight threatening diabetic retinopathy	2BBo.00
Foot abnormality - diabetes related	2G51000
O/E - Right diabetic foot at risk	2G5A.00
O/E - Left diabetic foot at risk	2G5B.00
Foot abnormality - diabetes related	2G5C.00
O/E - Right diabetic foot at low risk	2G5E.00
O/E - Right diabetic foot at moderate risk	2G5F.00
O/E - Right diabetic foot at high risk	2G5G.00
O/E - Right diabetic foot - ulcerated	2G5H.00
O/E - Left diabetic foot at low risk	2G5I.00
O/E - Left diabetic foot at moderate risk	2G5J.00
O/E - Left diabetic foot at high risk	2G5K.00
O/E - Left diabetic foot - ulcerated	2G5L.00
O/E - right chronic diabetic foot ulcer	2G5V.00
O/E - left chronic diabetic foot ulcer	2G5W.00
Pan retinal photocoagulation for diabetes	7276
Diabetes mellitus with ketoacidosis	C101.00
Diabetes mellitus, juvenile type, with ketoacidosis	C101000
Diabetes mellitus, adult onset, with ketoacidosis	C101100
Other specified diabetes mellitus with ketoacidosis	C101y00
Diabetes mellitus NOS with ketoacidosis	C101z00
Diabetes mellitus with hyperosmolar coma	C102.00
Diabetes mellitus, juvenile type, with hyperosmolar coma	C102000
Diabetes mellitus, adult onset, with hyperosmolar coma	C102100
Diabetes mellitus NOS with hyperosmolar coma	C102z00
Diabetes mellitus with ketoacidotic coma	C103.00
Diabetes mellitus, juvenile type, with ketoacidotic coma	C103000
Diabetes mellitus, adult onset, with ketoacidotic coma	C103100
Other specified diabetes mellitus with coma	C103y00
Diabetes mellitus NOS with ketoacidotic coma	C103z00
Diabetes mellitus with renal manifestation	C104.00
Diabetic nephropathy	C104.11

Diabetes mellitus, juvenile type, with renal manifestation	C104000
Diabetes mellitus, adult onset, with renal manifestation	C104100
Other specified diabetes mellitus with renal complications	C104y00
Diabetes mellitis with nephropathy NOS	C104z00
Diabetes mellitus with ophthalmic manifestation	C105.00
Diabetes mellitus, juvenile type, + ophthalmic manifestation	C105000
Diabetes mellitus, adult onset, + ophthalmic manifestation	C105100
Other specified diabetes mellitus with ophthalmic complicatn	C105y00
Diabetes mellitus NOS with ophthalmic manifestation	C105z00
Diabetes mellitus with neurological manifestation	C106.00
Diabetic amyotrophy	C106.11
Diabetes mellitus with neuropathy	C106.12
Diabetes mellitus with polyneuropathy	C106.13
Diabetes mellitus, juvenile, + neurological manifestation	C106000
Diabetes mellitus, adult onset, + neurological manifestation	C106100
Other specified diabetes mellitus with neurological comps	C106y00
Diabetes mellitus NOS with neurological manifestation	C106z00
Diabetes mellitus with peripheral circulatory disorder	C107.00
Diabetes mellitus with gangrene	C107.11
Diabetes with gangrene	C107.12
Diabetes mellitus, juvenile +peripheral circulatory disorder	C107000
Diabetes mellitus, adult, + peripheral circulatory disorder	C107100
Diabetes mellitus, adult with gangrene	C107200
IDDM with peripheral circulatory disorder	C107300
NIDDM with peripheral circulatory disorder	C107400
Other specified diabetes mellitus with periph circ comps	C107y00
Insulin-dependent diabetes mellitus with renal complications	C108000
Type I diabetes mellitus with renal complications	C108011
Type 1 diabetes mellitus with renal complications	C108012
Insulin-dependent diabetes mellitus with ophthalmic comps	C108100
Type I diabetes mellitus with ophthalmic complications	C108111
Type 1 diabetes mellitus with ophthalmic complications	C108112
Insulin-dependent diabetes mellitus with neurological comps	C108200
Type I diabetes mellitus with neurological complications	C108211
Type 1 diabetes mellitus with neurological complications	C108212
Insulin dependent diabetes mellitus with multiple complicatn	C108300
Type I diabetes mellitus with multiple complications	C108311
Type 1 diabetes mellitus with multiple complications	C108312
Insulin dependent diabetes mellitus with ulcer	C108500
Type I diabetes mellitus with ulcer	C108511
Type 1 diabetes mellitus with ulcer	C108512
Insulin dependent diabetes mellitus with gangrene	C108600
Type I diabetes mellitus with gangrene	C108611
Type 1 diabetes mellitus with gangrene	C108612
Insulin dependent diabetes mellitus with retinopathy	C108700
Type I diabetes mellitus with retinopathy	C108711

Type 1 diabetes mellitus with retinopathy	C108712
Insulin dependent diabetes mellitus with mononeuropathy	C108B00
Type I diabetes mellitus with mononeuropathy	C108B11
Type 1 diabetes mellitus with mononeuropathy	C108B12
Insulin dependent diabetes mellitus with polyneuropathy	C108C00
Type I diabetes mellitus with polyneuropathy	C108C11
Type 1 diabetes mellitus with polyneuropathy	C108C12
Insulin dependent diabetes mellitus with nephropathy	C108D00
Type I diabetes mellitus with nephropathy	C108D11
Type 1 diabetes mellitus with nephropathy	C108D12
Insulin dependent diabetes mellitus with hypoglycaemic coma	C108E00
Type I diabetes mellitus with hypoglycaemic coma	C108E11
Type 1 diabetes mellitus with hypoglycaemic coma	C108E12
Insulin dependent diabetes mellitus with diabetic cataract	C108F00
Type I diabetes mellitus with diabetic cataract	C108F11
Type 1 diabetes mellitus with diabetic cataract	C108F12
Insulin dependent diab mell with peripheral angiopathy	C108G00
Type I diabetes mellitus with peripheral angiopathy	C108G11
Type 1 diabetes mellitus with peripheral angiopathy	C108G12
Insulin dependent diabetes mellitus with arthropathy	C108H00
Type I diabetes mellitus with arthropathy	C108H11
Type 1 diabetes mellitus with arthropathy	C108H12
Insulin dependent diab mell with neuropathic arthropathy	C108J00
Type I diabetes mellitus with neuropathic arthropathy	C108J11
Type 1 diabetes mellitus with neuropathic arthropathy	C108J12
Other specified diabetes mellitus with multiple comps	C108y00
Unspecified diabetes mellitus with multiple complications	C108z00
Non-insulin-dependent diabetes mellitus with renal comps	C109000
Type II diabetes mellitus with renal complications	C109011
Type 2 diabetes mellitus with renal complications	C109012
Non-insulin-dependent diabetes mellitus with ophthalm comps	C109100
Type II diabetes mellitus with ophthalmic complications	C109111
Type 2 diabetes mellitus with ophthalmic complications	C109112
Non-insulin-dependent diabetes mellitus with neuro comps	C109200
Type II diabetes mellitus with neurological complications	C109211
Type 2 diabetes mellitus with neurological complications	C109212
Non-insulin-dependent diabetes mellitus with multiple comps	C109300
Type II diabetes mellitus with multiple complications	C109311
Type 2 diabetes mellitus with multiple complications	C109312
Non-insulin dependent diabetes mellitus with ulcer	C109400
Type II diabetes mellitus with ulcer	C109411
Type 2 diabetes mellitus with ulcer	C109412
Non-insulin dependent diabetes mellitus with gangrene	C109500
Type II diabetes mellitus with gangrene	C109511
Type 2 diabetes mellitus with gangrene	C109512
Non-insulin-dependent diabetes mellitus with retinopathy	C109600

Type II diabetes mellitus with retinopathy	C109611
Type 2 diabetes mellitus with retinopathy	C109612
Non-insulin dependent diabetes mellitus with mononeuropathy	C109A00
Type II diabetes mellitus with mononeuropathy	C109A11
Type 2 diabetes mellitus with mononeuropathy	C109A12
Non-insulin dependent diabetes mellitus with polyneuropathy	C109B00
Type II diabetes mellitus with polyneuropathy	C109B11
Type 2 diabetes mellitus with polyneuropathy	C109B12
Non-insulin dependent diabetes mellitus with nephropathy	C109C00
Type II diabetes mellitus with nephropathy	C109C11
Type 2 diabetes mellitus with nephropathy	C109C12
Non-insulin dependent diabetes mellitus with hypoglyca coma	C109D00
Type II diabetes mellitus with hypoglycaemic coma	C109D11
Type 2 diabetes mellitus with hypoglycaemic coma	C109D12
Non-insulin depend diabetes mellitus with diabetic cataract	C109E00
Type II diabetes mellitus with diabetic cataract	C109E11
Type 2 diabetes mellitus with diabetic cataract	C109E12
Non-insulin-dependent d m with peripheral angiopath	C109F00
Type II diabetes mellitus with peripheral angiopathy	C109F11
Type 2 diabetes mellitus with peripheral angiopathy	C109F12
Non-insulin dependent diabetes mellitus with arthropathy	C109G00
Type II diabetes mellitus with arthropathy	C109G11
Type 2 diabetes mellitus with arthropathy	C109G12
Non-insulin dependent d m with neuropathic arthropathy	C109H00
Type II diabetes mellitus with neuropathic arthropathy	C109H11
Type 2 diabetes mellitus with neuropathic arthropathy	C109H12
Hyperosmolar non-ketotic state in type 2 diabetes mellitus	C109K00
Malnutrition-related diabetes mellitus with coma	C10A000
Malnutrition-related diabetes mellitus with ketoacidosis	C10A100
Malnutrition-related diabetes mellitus with renal complicatn	C10A200
Malnutrit-related diabetes mellitus wth ophthalmic complicat	C10A300
Malnutrition-related diabetes mellitus wth neuro complicatns	C10A400
Malnutritn-relat diabetes melitus wth periph circul complctn	C10A500
Malnutrition-related diabetes mellitus with multiple comps	C10A600
Malnutrition-related diabetes mellitus without complications	C10A700
Malnutrit-related diabetes mellitus with unspec complics	C10AW00
Malnutrit-relat diabetes mellitus with other spec comps	C10AX00
Type 1 diabetes mellitus with renal complications	C10E000
Type I diabetes mellitus with renal complications	C10E011
Insulin-dependent diabetes mellitus with renal complications	C10E012
Type 1 diabetes mellitus with ophthalmic complications	C10E100
Type I diabetes mellitus with ophthalmic complications	C10E111
Insulin-dependent diabetes mellitus with ophthalmic comps	C10E112
Type 1 diabetes mellitus with neurological complications	C10E200
Type I diabetes mellitus with neurological complications	C10E211
Insulin-dependent diabetes mellitus with neurological comps	C10E212

Type 1 diabetes mellitus with multiple complications	C10E300
Type I diabetes mellitus with multiple complications	C10E311
Insulin dependent diabetes mellitus with multiple complicat	C10E312
Type 1 diabetes mellitus with ulcer	C10E500
Type I diabetes mellitus with ulcer	C10E511
Insulin dependent diabetes mellitus with ulcer	C10E512
Type 1 diabetes mellitus with gangrene	C10E600
Type I diabetes mellitus with gangrene	C10E611
Insulin dependent diabetes mellitus with gangrene	C10E612
Type 1 diabetes mellitus with retinopathy	C10E700
Type I diabetes mellitus with retinopathy	C10E711
Insulin dependent diabetes mellitus with retinopathy	C10E712
Type 1 diabetes mellitus with mononeuropathy	C10EB00
Type I diabetes mellitus with mononeuropathy	C10EB11
Insulin dependent diabetes mellitus with mononeuropathy	C10EB12
Type 1 diabetes mellitus with polyneuropathy	C10EC00
Type I diabetes mellitus with polyneuropathy	C10EC11
Insulin dependent diabetes mellitus with polyneuropathy	C10EC12
Type 1 diabetes mellitus with nephropathy	C10ED00
Type I diabetes mellitus with nephropathy	C10ED11
Insulin dependent diabetes mellitus with nephropathy	C10ED12
Type 1 diabetes mellitus with hypoglycaemic coma	C10EE00
Type I diabetes mellitus with hypoglycaemic coma	C10EE11
Insulin dependent diabetes mellitus with hypoglycaemic coma	C10EE12
Type 1 diabetes mellitus with diabetic cataract	C10EF00
Type I diabetes mellitus with diabetic cataract	C10EF11
Insulin dependent diabetes mellitus with diabetic cataract	C10EF12
Type 1 diabetes mellitus with peripheral angiopathy	C10EG00
Type I diabetes mellitus with peripheral angiopathy	C10EG11
Insulin dependent diab mell with peripheral angiopathy	C10EG12
Type 1 diabetes mellitus with arthropathy	C10EH00
Type I diabetes mellitus with arthropathy	C10EH11
Insulin dependent diabetes mellitus with arthropathy	C10EH12
Type 1 diabetes mellitus with neuropathic arthropathy	C10EJ00
Type I diabetes mellitus with neuropathic arthropathy	C10EJ11
Insulin dependent diab mell with neuropathic arthropathy	C10EJ12
Type 1 diabetes mellitus with persistent proteinuria	C10EK00
Type I diabetes mellitus with persistent proteinuria	C10EK11
Type 1 diabetes mellitus with persistent microalbuminuria	C10EL00
Type I diabetes mellitus with persistent microalbuminuria	C10EL11
Type 1 diabetes mellitus with ketoacidosis	C10EM00
Type I diabetes mellitus with ketoacidosis	C10EM11
Type 1 diabetes mellitus with ketoacidotic coma	C10EN00
Type I diabetes mellitus with ketoacidotic coma	C10EN11
Type 1 diabetes mellitus with exudative maculopathy	C10EP00
Type I diabetes mellitus with exudative maculopathy	C10EP11

Type 2 diabetes mellitus with renal complications	C10F000
Type II diabetes mellitus with renal complications	C10F011
Type 2 diabetes mellitus with ophthalmic complications	C10F100
Type II diabetes mellitus with ophthalmic complications	C10F111
Type 2 diabetes mellitus with neurological complications	C10F200
Type II diabetes mellitus with neurological complications	C10F211
Type 2 diabetes mellitus with multiple complications	C10F300
Type II diabetes mellitus with multiple complications	C10F311
Type 2 diabetes mellitus with ulcer	C10F400
Type II diabetes mellitus with ulcer	C10F411
Type 2 diabetes mellitus with gangrene	C10F500
Type II diabetes mellitus with gangrene	C10F511
Type 2 diabetes mellitus with retinopathy	C10F600
Type II diabetes mellitus with retinopathy	C10F611
Type 2 diabetes mellitus with mononeuropathy	C10FA00
Type II diabetes mellitus with mononeuropathy	C10FA11
Type 2 diabetes mellitus with polyneuropathy	C10FB00
Type II diabetes mellitus with polyneuropathy	C10FB11
Type 2 diabetes mellitus with nephropathy	C10FC00
Type II diabetes mellitus with nephropathy	C10FC11
Type 2 diabetes mellitus with hypoglycaemic coma	C10FD00
Type II diabetes mellitus with hypoglycaemic coma	C10FD11
Type 2 diabetes mellitus with diabetic cataract	C10FE00
Type II diabetes mellitus with diabetic cataract	C10FE11
Type 2 diabetes mellitus with peripheral angiopathy	C10FF00
Type II diabetes mellitus with peripheral angiopathy	C10FF11
Type 2 diabetes mellitus with arthropathy	C10FG00
Type II diabetes mellitus with arthropathy	C10FG11
Type 2 diabetes mellitus with neuropathic arthropathy	C10FH00
Type II diabetes mellitus with neuropathic arthropathy	C10FH11
Hyperosmolar non-ketotic state in type 2 diabetes mellitus	C10FK00
Type 2 diabetes mellitus with persistent proteinuria	C10FL00
Type II diabetes mellitus with persistent proteinuria	C10FL11
Type 2 diabetes mellitus with persistent microalbuminuria	C10FM00
Type II diabetes mellitus with persistent microalbuminuria	C10FM11
Type 2 diabetes mellitus with ketoacidosis	C10FN00
Type II diabetes mellitus with ketoacidosis	C10FN11
Type 2 diabetes mellitus with ketoacidotic coma	C10FP00
Type II diabetes mellitus with ketoacidotic coma	C10FP11
Type 2 diabetes mellitus with exudative maculopathy	C10FQ00
Type II diabetes mellitus with exudative maculopathy	C10FQ11
Other specified diabetes mellitus with other spec comps	C10yy00
Diabetes mellitus NOS with other specified manifestation	C10yz00
Diabetes mellitus with unspecified complication	C10z.00
Diabetes mellitus, juvenile type, + unspecified complication	C10z000
Diabetes mellitus, adult onset, + unspecified complication	C10z100

Other specified diabetes mellitus with unspecified comps	C10zy00
Diabetes mellitus NOS with unspecified complication	C10zz00
[X]Malnutrit-relat diabetes mellitus with other spec comps	Cyu2100
[X]Malnutrit-related diabetes mellitus with unspec complics	Cyu2200
[X]Unspecified diabetes mellitus with renal complications	Cyu2300
[X]Glomerular disorders in diabetes mellitus	Kyu0300

Table j-xiii Codes for Any tumour

description	medcode
Malignant neoplasm of eye	B50..00
Malignant neoplasm of brain	B51..00
Cerebral tumour - malignant	B51..11
Malig neop of other and unspecified parts of nervous system	B52..00
Malignant neoplasm of thyroid gland	B53..00
Malig neop of other endocrine glands and related structures	B54..00
Malignant neoplasm of other and ill-defined sites	B55..00
Malignant neoplasm of unspecified site	B59..00
Malignant neoplasm of other and unspecified site OS	B5y..00
Malignant neoplasm of other and unspecified site NOS	B5z..00
Malignant neoplasms of lymphoid and histiocytic tissue NOS	B62z.00
Benign neoplasm of parotid gland	B702000
Adenoma of parotid gland	B702011
Benign neoplasm of submandibular gland	B702100
Benign neoplasm of sublingual gland	B702200
Warthin's tumour	B702300
Benign neoplasm of major salivary gland NOS	B702z00
Benign islet cell tumour	B717000
Endocrine tumour of pancreas	B717011
Benign neoplasm of islets of Langerhans NOS	B717z00
Benign neoplasm of brain	B7F0.00
Cerebral tumour - benign	B7F0.11
Benign neoplasm of cranial nerves	B7F1.00
Benign neoplasm of cerebral meninges	B7F2.00
Benign neoplasm of spinal cord	B7F3.00
Benign neoplasm of spinal meninges	B7F4.00
Benign neoplasm of meninges, unspecified	B7FX.00
Benign neoplasm of other part of nervous system	B7Fy.00
Benign neoplasm of brain or other nervous system NOS	B7Fz.00
Haemangioma	B7J0.00
Glomus tumour	B7J0.11
Lymphangioma	B7J1.00
Congenital lymphangioma	B7J1.11
Naevus - lymphatic	B7J1.12
Haemangioma or lymphangioma NOS	B7Jz.00
Neoplasm of uncertain behaviour of parotid gland	B900000
Mixed parotid tumour	B900011
Neoplasm of uncertain behaviour of sublingual gland	B900100
Neoplasm of uncertain behaviour of submandibular gland	B900200
Neoplasm of uncertain behaviour of major salivary gland NOS	B900z00
Neop of uncertain behaviour of bone and articular cartilage	B930.00
Neop of uncertain behaviour connective and other soft tissue	B931.00
Neoplasm of uncertain behaviour of skin	B932.00

Neoplasm of uncertain behaviour of breast	B933.00
Cystosarcoma phyllodes	B933.11
Neoplasm of uncertain behaviour of histiocytic and mast cell	B935.00
Histiocytic tumour NOS	B935.11
Mastocytoma NOS	B935.12
Neoplasm of uncertain behaviour of plasma cells	B936.00
Myeloma - solitary	B936.11
Plasmacytoma NOS	B936.12
Neop uncertain behaviour other lymphatic/haematopoietic tiss	B937.00
Neoplasm of uncertain behaviour of blood	B937.11
Neo/uncertn+unknwn behav/lymph,h'matopetc+rel tiss,unspcf	B93X.00
Neoplasm of uncertain behaviour of other specified sites	B93y.00
Neop uncertain behaviour other unspec site and tissue NOS	B93z.00
[M]Tumour morphology	BB...11
[M]Neoplasms NOS	BB0..00
[M]Neoplasm, benign	BB00.00
[M]Neoplasm, uncertain whether benign or malignant	BB01.00
[M]Neoplasm, malignant	BB02.00
[M]Neoplasm, metastatic	BB03.00
[M]Secondary neoplasm	BB03.11
[M]Neoplasm, malig, uncertain whether primary or metastatic	BB04.00
[M]Tumour cells, benign	BB05.00
[M]Tumour cells, uncertain whether benign or malignant	BB06.00
[M]Tumour cells, malignant	BB07.00
[M]Malignant tumour, small cell type	BB08.00
[M]Malignant tumour, giant cell type	BB09.00
[M]Malignant tumour, fusiform cell type	BB0A.00
[M]Unspecified tumour cell NOS	BB0z.00
[M]Epithelial neoplasms NOS	BB1..00
[M]Epithelial tumour, benign	BB10.00
[M]Carcinoma in situ NOS	BB11.00
[M]Intraepithelial carcinoma NOS	BB11.11
[M]Carcinoma NOS	BB12.00
[M]Carcinoma, metastatic, NOS	BB13.00
[M]Secondary carcinoma	BB13.11
[M]Carcinomatosis	BB14.00
[M]Epithelioma, benign	BB15.00
[M]Epithelioma, malignant	BB16.00
[M]Large cell carcinoma NOS	BB17.00
[M]Carcinoma, undifferentiated type, NOS	BB18.00
[M]Carcinoma, anaplastic type, NOS	BB19.00
[M]Pleomorphic carcinoma	BB1A.00
[M]Giant cell and spindle cell carcinoma	BB1B.00
[M]Giant cell carcinoma	BB1C.00
[M]Spindle cell carcinoma	BB1D.00
[M]Pseudosarcomatous carcinoma	BB1E.00

[M]Polygonal cell carcinoma	BB1F.00
[M]Spheroidal cell carcinoma	BB1G.00
[M]Small cell carcinoma NOS	BB1J.00
[M]Reserve cell carcinoma	BB1J.11
[M]Round cell carcinoma	BB1J.12
[M]Oat cell carcinoma	BB1K.00
[M]Small cell carcinoma, fusiform cell type	BB1L.00
[M]Small cell carcinoma, intermediate cell	BB1M.00
[M]Small cell-large cell carcinoma	BB1N.00
[M]Unspecified epithelial neoplasm	BB1z.00
[M]Papillary and squamous cell neoplasms	BB2..00
[M]Papillary neoplasms	BB2..11
[M]Squamous cell neoplasms	BB2..12
[M]Basal cell neoplasms	BB3..00
[M]Basal cell tumour	BB30.00
[M]Basal cell carcinoma NOS	BB31.00
[M]Multicentric basal cell carcinoma	BB32.00
[M]Basal cell carcinoma, morphoea type	BB33.00
[M]Basal cell carcinoma, fibroepithelial type	BB34.00
[M]Basosquamous carcinoma	BB35.00
[M]Metatypical carcinoma	BB36.00
[M]Intraepidermal epithelioma of Jadassohn	BB37.00
[M]Trichoepithelioma	BB38.00
[M]Brooke's tumour	BB38.11
[M]Epithelioma adenoides cyst	BB38.12
[M]Trichofolliculoma	BB39.00
[M]Tricholemmoma	BB3A.00
[M]Pilomatrixoma	BB3B.00
[M]Malherbe's calcified epithelioma	BB3B.11
[M]Basal cell neoplasm NOS	BB3z.00
[M]Transitional cell papillomas and carcinomas	BB4..00
[M]Adenomas and adenocarcinomas	BB5..00
[M]Adenocarcinomas	BB5..11
[M]Adenomas	BB5..12
[M]Adenoma NOS	BB50.00
[M]Adenocarcinoma in situ	BB51.00
[M]Adenocarcinoma NOS	BB52.00
[M]Adenocarcinoma, metastatic, NOS	BB53.00
[M]Scirrhous adenocarcinoma	BB54.00
[M]Linitis plastica	BB55.00
[M]Superficial spreading adenocarcinoma	BB56.00
[M]Adenocarcinoma, intestinal type	BB57.00
[M]Carcinoma, diffuse type	BB58.00
[M]Monomorphic adenoma	BB59.00
[M]Basal cell adenoma	BB5A.00
[M]Pancreatic adenomas and carcinomas	BB5B.00

[M]Islet cell adenoma	BB5B000
[M]Nesidioblastoma	BB5B011
[M]Islet cell carcinoma	BB5B100
[M]Insulinoma NOS	BB5B200
[M]Beta-cell adenoma	BB5B211
[M]Insulinoma, malignant	BB5B300
[M]Beta-cell tumour, malignant	BB5B311
[M]Glucagonoma NOS	BB5B400
[M]Alpha-cell adenoma	BB5B411
[M]Glucagonoma, malignant	BB5B500
[M]Alpha-cell tumour,malignant	BB5B511
[M]Mixed islet cell and exocrine adenocarcinoma	BB5B600
[M]Pancreatic adenoma or carcinoma NOS	BB5Bz00
[M]Gastrinoma and carcinomas	BB5C.00
[M]Gastrinoma NOS	BB5C000
[M]G cell tumour NOS	BB5C011
[M]Gastrinoma, malignant	BB5C100
[M]G cell tumour, malignant	BB5C111
[M]Gastrinoma or carcinoma NOS	BB5Cz00
[M]Hepatobiliary tract adenomas and carcinomas	BB5D.00
[M]Biliary tract adenomas and adenocarcinomas	BB5D.11
[M]Trabecular adenoma	BB5E.00
[M]Trabecular adenocarcinoma	BB5F.00
[M]Embryonal adenoma	BB5G.00
[M]Eccrine dermal cylindroma	BB5H.00
[M]Turban tumour	BB5H.11
[M]Adenoid cystic carcinoma	BB5J.00
[M]Cylindroid adenocarcinoma	BB5J.11
[M]Cylindroid bronchial adenoma	BB5J.12
[M]Cylindroma NOS	BB5J.13
[M]Cribriform carcinoma	BB5K.00
[M]Adenomatous and adenocarcinomatous polyps	BB5L.00
[M]Tubular adenomas and adenocarcinomas	BB5M.00
[M]Adenomatous and adenocarcinomatous polyps of colon	BB5N.00
[M]Adenoma or or adenocarcinoma in polyposis coli	BB5N.11
[M]Solid carcinoma NOS	BB5P.00
[M]Carcinoma simplex	BB5Q.00
[M]Carcinoid tumours	BB5R.00
[M]Carcinoid tumour NOS	BB5R000
[M]Carcinoid tumour, malignant	BB5R100
[M]Carcinoid bronchial adenoma	BB5R111
[M]Carcinoid tumour, argentaffin, NOS	BB5R200
[M]Argentaffinoma NOS	BB5R211
[M]Carcinoid tumour, argentaffin, malignant	BB5R300
[M]Carcinoid tumour, nonargentaffin, NOS	BB5R400
[M]Carcinoid tumour, nonargentaffin, malignant	BB5R500

[M]Mucocarcinoid tumour, malignant	BB5R600
[M]Goblet cell tumour	BB5R611
[M]Composite carcinoid	BB5R700
[M]Adenocarcinoid tumour	BB5R800
[M]Neuroendocrine carcinoma	BB5R900
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[M]Respiratory tract adenomas and adenocarcinomas	BB5S.00
[M]Papillary adenomas and adenocarcinomas	BB5T.00
[M]Villous adenomas and adenocarcinomas	BB5U.00
[M]Pituitary adenomas and carcinomas	BB5V.00
[M]Oxyphilic adenomas and adenocarcinomas	BB5W.00
[M]Clear cell adenomas and adenocarcinomas	BB5X.00
[M]Hypernephroid tumour	BB5Y.00
[M]Clear cell adenofibroma	BB5Z.00
[M]Renal adenoma and carcinoma	BB5a.00
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[M]Grawitz tumour	BB5a011
[M]Hypernephroma	BB5a012
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[M]Renal adenoma or carcinoma NOS	BB5az00
[M]Granular cell carcinoma	BB5b.00
[M]Parathyroid adenomas and adenocarcinomas	BB5c.00
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[M]Thyroid adenoma and adenocarcinoma	BB5f.00
[M]Multiple endocrine adenomas	BB5g.00
[M]Adrenal cortical tumours	BB5h.00
[M]Adrenal cortical adenoma NOS	BB5h000
[M]Adrenal cortical carcinoma	BB5h100
[M]Adrenal cortical adenoma, compact cell type	BB5h200
[M]Adrenal cortical adenoma, heavily pigmented variant	BB5h300
[M]Black adenoma	BB5h311
[M]Adrenal cortical adenoma, clear cell type	BB5h400
[M]Adrenal cortical adenoma, glomerulosa cell type	BB5h500
[M]Adrenal cortical adenoma, mixed cell type	BB5h600
[M]Adrenal cortical tumours NOS	BB5hz00
[M]Endometrioid adenomas and carcinomas	BB5j.00
[M]Adenoma and adenocarcinoms OS	BB5y.00
[M]Basal cell adenocarcinoma	BB5y000
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[M]Klatskin's tumour	BB5y200
[M]Apudoma	BB5y300
[M]Prolactinoma	BB5y400
[M]Lipid-rich carcinoma	BB5y500

[M]Glycogen-rich carcinoma	BB5y600
[M]Adenoma or adenocarcinoma NOS	BB5z.00
[M]Adnexal and skin appendage neoplasms	BB6..00
[M]Sweat gland adenoma	BB61000
[M]Hidradenoma NOS	BB61011
[M]Nodular hidradenoma	BB61012
[M]Syringadenoma NOS	BB61013
[M]Sweat gland tumour NOS	BB61100
[M]Sweat gland adenocarcinoma	BB61200
[M]Sweat gland adenoma or adenocarcinoma NOS	BB61z00
[M]Mucoepidermoid neoplasms	BB7..00
[M]Mucoepidermoid tumour	BB70.00
[M]Mucoepidermoid carcinoma	BB71.00
[M]Mucoepidermoid neoplasm NOS	BB7z.00
[M]Cystic, mucinous and serous neoplasms	BB8..00
[M]Cystadenoma and carcinoma	BB80.00
[M]Ovarian cystic, mucinous and serous neoplasms	BB81.00
[M]Ovarian cystadenoma or carcinoma	BB81.11
[M]Ovarian mucinous tumour	BB81.12
[M]Ovarian papillary tumour	BB81.13
[M]Ovarian serous tumour	BB81.14
[M]Serous cystadenoma NOS	BB81000
[M]Serous cystadenoma, borderline malignancy	BB81100
[M]Serous cystadenocarcinoma, NOS	BB81200
[M]Papillary cystadenoma NOS	BB81300
[M]Papillary cystadenoma, borderline malignancy	BB81400
[M]Papillary cystadenocarcinoma, NOS	BB81500
[M]Papillary serous cystadenoma NOS	BB81600
[M]Papillary serous cystadenoma, borderline malignancy	BB81700
[M]Papillary serous cystadenocarcinoma	BB81800
[M]Serous surface papilloma NOS	BB81900
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[M]Mucinous cystadenocarcinoma NOS	BB81E00
[M]Pseudomucinous adenocarcinoma	BB81E11
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[M]Papillary mucinous cystadenocarcinoma	BB81H00
[M]Serous cystadenoma, borderline malignancy	BB81J00
[M]Papillary cystadenoma, borderline malignancy	BB81K00
[M]Papillary cystic tumour	BB81L00
[M]Papillary serous cystadenoma, borderline malignancy	BB81M00
[M]Ovarian cystic, mucinous or serous neoplasm NOS	BB81z00

[M]Mucinous adenoma and adenocarcinoma	BB82.00
[M]Pseudomyxoma peritonei	BB83.00
[M]Mucin-producing adenocarcinoma	BB84.00
[M]Signet ring carcinoma	BB85.00
[M]Signet ring cell carcinoma	BB85000
[M]Metastatic signet ring cell carcinoma	BB85100
[M]Krukenberg tumour	BB85111
[M]Signet ring carcinoma NOS	BB85z00
[M]Cystic, mucinous or serous neoplasm NOS	BB8z.00
[M]Ductal, lobular and medullary neoplasms	BB9..00
[M]Acinar cell neoplasms	BBA..00
[M]Acinar cell adenoma	BBA0.00
[M]Acinar cell tumour	BBA1.00
[M]Acinar cell carcinoma	BBA2.00
[M]Acinar cell neoplasm NOS	BBAz.00
[M]Complex epithelial neoplasms	BBB..00
[M]Adenosquamous carcinoma	BBB0.00
[M]Adenolymphoma	BBB1.00
[M]Warthin's tumour	BBB1.11
[M]Adenocarcinoma with squamous metaplasia	BBB2.00
[M]Adenoacanthoma	BBB2.11
[M]Adenocarcinoma with cartilaginous and osseous metaplasia	BBB3.00
[M]Adenocarcinoma with spindle cell metaplasia	BBB4.00
[M]Adenocarcinoma with apocrine metaplasia	BBB5.00
[M]Thymoma	BBB6.00
[M]Epithelial-myoepithelial carcinoma	BBB7.00
[M]Complex epithelial neoplasm NOS	BBBz.00
[M]Specialised gonadal neoplasms	BBC..00
[M]Sex cord-stromal tumour	BBC0.00
[M]Gonadal stromal tumour	BBC0.11
[M]Ovarian stromal tumour	BBC0.12
[M]Testicular stromal tumour	BBC0.13
[M]Sex cord tumour with annular tubules	BBC0000
[M]Thecal cell neoplasms	BBC1.00
[M]Luteoma NOS	BBC2.00
[M]Luteinoma	BBC2.11
[M]Granulosa cell tumour NOS	BBC3.00
[M]Juvenile granulosa cell tumour	BBC3000
[M]Granulosa cell tumour, malignant	BBC4.00
[M]Granulosa cell-theca cell tumour	BBC5.00
[M]Androblastoma	BBC6.00
[M]Sertoli-Leydig cell tumour	BBC7.00
[M]Gynandroblastoma	BBC8.00
[M]Tubular androblastoma NOS	BBC9.00
[M]Pick's tubular adenoma	BBC9.11
[M]Sertoli cell adenoma	BBC9.12

[M]Sertoli cell tumour	BBC9.13
[M]Testicular adenoma	BBC9.14
[M]Sertoli cell carcinoma	BBCA.00
[M]Tubular androblastoma with lipid storage	BBCB.00
[M]Sertoli cell tumour with lipid storage	BBCB.11
[M]Leydig cell tumour	BBCC.00
[M]Leydig cell tumour, benign	BBCC000
[M]Interstitial cell tumour, benign	BBCC011
[M]Leydig cell tumour, malignant	BBCC100
[M]Interstitial cell tumour, malignant	BBCC111
[M]Leydig cell tumour NOS	BBCCz00
[M]Interstitial cell tumour NOS	BBCCz11
[M]Hilar cell tumour	BBCD.00
[M]Lipid cell tumour of ovary	BBCE.00
[M]Masculinovoblastoma	BBCE.11
[M]Adrenal rest tumour	BBCF.00
[M]Sclerosing stromal tumour	BBCG.00
[M]Specialised gonadal neoplasm NOS	BBCz.00
[M]Paragangliomas and glomus tumours	BBD..00
[M]Paraganglioma NOS	BBD0.00
[M]Paraganglioma, malignant	BBD1.00
[M]Sympathetic paraganglioma	BBD2.00
[M]Parasympathetic paraganglioma	BBD3.00
[M]Glomus jugulare tumour	BBD4.00
[M]Jugular paraganglioma	BBD4.11
[M]Aortic body tumour	BBD5.00
[M]Carotid body tumour	BBD6.00
[M]Extra-adrenal paraganglioma, NOS	BBD7.00
[M]Chemodectoma	BBD7.11
[M]Extra-adrenal paraganglioma, malignant	BBD8.00
[M]Phaeochromocytoma NOS	BBD9.00
[M]Chromaffin paraganglioma	BBD9.11
[M]Chromaffin tumour	BBD9.12
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[M]Phaeochromocytoma, malignant	BBDA.00
[M]Phaeochromoblastoma	BBDA.11
[M]Glomangiosarcoma	BBDB.00
[M]Glomoid sarcoma	BBDB.11
[M]Glomus tumour	BBDC.00
[M]Glomangioma	BBDD.00
[M]Gangliocytic paraganglioma	BBDE.00
[M]Glomangiomyoma	BBDF.00
[M]Paraganglioma or glomus tumour NOS	BBDz.00
[M]Naevi and melanomas	BBE..00
[M]Soft tissue tumours and sarcomas NOS	BBF..00
[M]Soft tissue tumour, benign	BBF0.00

[M]Sarcoma NOS	BBF1.00
[M]Sarcomatosis NOS	BBF2.00
[M]Spindle cell sarcoma	BBF3.00
[M]Giant cell sarcoma (except of bone)	BBF4.00
[M]Pleomorphic cell sarcoma	BBF4.11
[M]Small cell sarcoma	BBF5.00
[M]Round cell sarcoma	BBF5.11
[M]Epithelioid cell sarcoma	BBF6.00
[M]Soft tissue tumour or sarcoma NOS	BBFz.00
[M]Fibromatous neoplasms	BBG..00
[M]Myxomatous neoplasms	BBH..00
[M]Lipomatous neoplasms	BBJ..00
[M]Lipoma NOS	BBJ0.00
[M]Liposarcoma NOS	BBJ1.00
[M]Fibroliposarcoma	BBJ1.11
[M]Fibrolipoma	BBJ2.00
[M]Fibroma molle	BBJ2.11
[M]Soft fibroma	BBJ2.12
[M]Liposarcoma, well differentiated type	BBJ3.00
[M]Fibromyxolipoma	BBJ4.00
[M]Myxolipoma	BBJ4.11
[M]Myxoid liposarcoma	BBJ5.00
[M]Embryonal liposarcoma	BBJ5.11
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[M]Round cell liposarcoma	BBJ6.00
[M]Pleomorphic liposarcoma	BBJ7.00
[M]Mixed type liposarcoma	BBJ8.00
[M]Intramuscular lipoma	BBJ9.00
[M]Infiltrating lipoma	BBJ9.11
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[M]Angiolipomatous neoplasms	BBJB.00
[M]Myelolipoma	BBJC.00
[M]Hibernoma	BBJD.00
[M]Brown fat tumour	BBJD.11
[M]Fetal fat cell lipoma	BBJD.12
[M]Lipoblastomatosis	BBJE.00
[M]Fetal lipoma NOS	BBJE.11
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[M]Lipomatous neoplasms NOS	BBJz.00
[M]Myomatous neoplasms	BBK..00
[M]Rhabdomyoma NOS	BBK3000
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[M]Pleomorphic rhabdomyosarcoma	BBK3200
[M]Mixed cell rhabdomyosarcoma	BBK3300
[M]Fetal rhabdomyoma	BBK3400

[M]Adult rhabdomyoma	BBK3500
[M]Glycogenic rhabdomyoma	BBK3511
[M]Embryonal rhabdomyosarcoma	BBK3600
[M]Sarcoma botryoides	BBK3611
[M]Alveolar rhabdomyosarcoma	BBK3700
[M]Smooth muscle tumour NOS	BBK3800
[M]Rhabdomyomatous neoplasm NOS	BBK3z00
[M]Complex mixed and stromal neoplasms	BBL..00
[M]Endometrial stromal sarcoma	BBL0.00
[M]Endolymphatic stromal myosis	BBL1.00
[M]Stromal endometriosis	BBL1.11
[M]Adenomyoma	BBL2.00
[M]Pleomorphic adenoma	BBL3.00
[M]Chondroid syringoma	BBL3.11
[M]Mixed tumour NOS	BBL3.12
[M]Mixed tumour, malignant, NOS	BBL4.00
[M]Mullerian mixed tumour	BBL5.00
[M]Mesodermal mixed tumour	BBL6.00
[M]Mixed and stromal renal neoplasms	BBL7.00
[M]Nephromas and nephroblastomas	BBL7.11
[M]Mesoblastic nephroma	BBL7000
[M]Nephroblastoma NOS	BBL7100
[M]Adenosarcoma	BBL7111
[M]Wilms' tumour	BBL7112
[M]Epithelial nephroblastoma	BBL7200
[M]Mesenchymal nephroblastoma	BBL7300
[M]Mixed or stromal renal neoplasm NOS	BBL7z00
[M]Hepatoblastoma	BBL8.00
[M]Embryonal hepatoma	BBL8.11
[M]Carcinosarcoma NOS	BBL9.00
[M]Carcinosarcoma, embryonal type	BBLA.00
[M]Pneumoblastoma	BBLA.11
[M]Myoepithelioma	BBLB.00
[M]Mesenchymomas	BBLC.00
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[M]Adenosarcoma	BBLE.00
[M]Endometrial stromal nodule	BBLF.00
[M]Carcinoma in pleomorphic adenoma	BBLG.00
[M]Rhabdoid sarcoma	BBLH.00
[M]Clear cell sarcoma of kidney	BBLJ.00
[M]Pancreatoblastoma	BBLK.00
[M]Pulmonary blastoma	BBLM.00
[M]Complex mixed or stromal neoplasm NOS	BBLz.00
[M]Fibroepithelial neoplasms	BBM..00
[M]Brenner tumours	BBM0.00
[M]Brenner tumour, borderline malignancy	BBM0000

[M]Brenner tumour, malignant	BBM0100
[M]Brenner tumour NOS	BBM0z00
[M]Fibroadenoma NOS	BBM1.00
[M]Intracanalicular fibroadenoma NOS	BBM2.00
[M]Pericanalicular fibroadenoma	BBM3.00
[M]Adenofibroma NOS	BBM4.00
[M]Cystadenofibroma NOS	BBM4.11
[M]Serous adenofibroma	BBM5.00
[M]Mucinous adenofibroma	BBM6.00
[M]Cellular intracanalicular fibroadenoma	BBM7.00
[M]Cystosarcoma phyllodes, benign	BBM7.11
[M]Fibroadenoma phyllodes	BBM7.12
[M]Giant fibroadenoma NOS	BBM7.13
[M]Giant intracanalicular fibroadedoma	BBM7.14
[M]Cystosarcoma phyllodes NOS	BBM8.00
[M]Cystosarcoma phyllodes, malignant	BBM9.00
[M]Juvenile fibroadenoma	BBMA.00
[M]Giant fibroadenoma	BBMB.00
[M]Fibroepithelial neoplasm NOS	BBMz.00
[M]Synovial neoplasms	BBN..00
[M]Mesothelial neoplasms	BBP..00
[M]Mesothelioma, benign	BBP0.00
[M]Mesothelioma, malignant	BBP1.00
[M]Fibrous mesothelioma, benign	BBP2.00
[M]Fibrous mesothelioma, malignant	BBP3.00
[M]Epithelioid mesothelioma, benign	BBP4.00
[M]Epithelioid mesothelioma, malignant	BBP5.00
[M]Mesothelioma, biphasic type, benign	BBP6.00
[M]Mesothelioma, biphasic type, malignant	BBP7.00
[M]Adenomatoid tumour NOS	BBP8.00
[M]Cystic mesothelioma	BBP9.00
[M]Mesothelioma, unspecified	BBPX.00
[M]Mesothelial neoplasm NOS	BBPz.00
[M]Germ cell neoplasms	BBQ..00
[M]Dysgerminoma	BBQ0.00
[M]Seminomas	BBQ1.00
[M]Germinoma	BBQ2.00
[M]Embryonal carcinoma NOS	BBQ3.00
[M]Endodermal sinus tumour	BBQ4.00
[M]Infantile embryonal carcinoma	BBQ4.11
[M]Orchioblastoma	BBQ4.12
[M]Polyvesicular vitelline tumour	BBQ4.13
[M]Yolk sac tumour	BBQ4.14
[M]Polyembryoma	BBQ5.00
[M]Polyembryonal embryonal carcinoma	BBQ5.11
[M]Gonadoblastoma	BBQ6.00

[M]Gonocytoma	BBQ6.11
[M]Teratomas	BBQ7.00
[M]Dermoid cyst	BBQ8.00
[M]Dermoid NOS	BBQ8.11
[M]Dermoid cyst with malignant transformation	BBQ9.00
[M]Strumal neoplasms	BBQA.00
[M]Mixed germ cell tumour	BBQB.00
[M]Germ cell neoplasm NOS	BBQz.00
[M]Trophoblastic neoplasms	BBR..00
[M]Hydatidiform mole NOS	BBR0.00
[M]Hydatid mole	BBR0.11
[M]Invasive hydatidiform mole	BBR1.00
[M]Chorioadenoma	BBR1.11
[M]Chorioadenoma destruens	BBR1.12
[M]Invasive mole NOS	BBR1.13
[M]Choriocarcinoma	BBR2.00
[M]Chorioepithelioma	BBR2.11
[M]Choriocarcinoma combined with teratoma	BBR3.00
[M]Malignant teratoma, trophoblastic	BBR4.00
[M]Partial hydatidiform mole	BBR5.00
[M]Placental site trophoblastic tumour	BBR6.00
[M]Classical hydatidiform mole	BBR7.00
[M]Complete hydatidiform mole	BBR8.00
[M]Trophoblastic neoplasm NOS	BBRz.00
[M]Mesonephromas	BBS..00
[M]Mesonephroma, benign	BBS0.00
[M]Wolffian duct adenoma	BBS0.11
[M]Mesonephric tumour	BBS1.00
[M]Mesonephroma, malignant	BBS2.00
[M]Wolffian duct carcinoma	BBS2.11
[M]Endosalpingioma	BBS3.00
[M]Mesonephroma NOS	BBSz.00
[M]Blood vessel tumours	BBT..00
[M]Haemangiomatous tumours	BBT..11
[M]Haemangioma NOS	BBT0.00
[M]Angioma NOS	BBT0.11
[M]Chorioangioma	BBT0.12
[M]Haemangiosarcoma	BBT1.00
[M]Angiosarcoma	BBT1.11
[M]Cavernous haemangioma	BBT2.00
[M]Venous haemangioma	BBT3.00
[M]Racemose haemangioma	BBT4.00
[M]Arteriovenous haemangioma	BBT4.11
[M]Kupffer cell sarcoma	BBT5.00
[M]Haemangioendothelioma	BBT7.00
[M]Capillary haemangioma	BBT8.00

[M]Haemangioma simplex	BBT8.11
[M]Infantile haemangioma	BBT8.12
[M]Juvenile haemangioma	BBT8.13
[M]Plexiform haemangioma	BBT8.14
[M]Intramuscular haemangioma	BBT9.00
[M]Kaposi's sarcoma	BBTA.00
[M]Multiple haemorrhagic sarcoma	BBTA.11
[M]Angiokeratoma	BBTB.00
[M]Verrucous keratotic haemangioma	BBTC.00
[M]Haemangiopericytic neoplasms	BBTD.00
[M]Angiofibroma NOS	BBTE.00
[M]Juvenile angiofibroma	BBTE.11
[M]Haemangioblastoma	BBTF.00
[M]Angioblastoma	BBTF.11
[M]Epithelioid haemangioma	BBTG.00
[M]Histiocytoid haemangioma	BBTH.00
[M]Epithelioid haemangioendothelioma NOS	BBTJ.00
[M]Epithelioid haemangioendothelioma, malignant	BBTK.00
[M]Intravascular bronchial alveolar tumour	BBTL.00
[M]Blood vessel tumour NOS	BBTz.00
[M]Lymphatic vessel tumours	BBU..00
[M]Lymphangiomatous tumours	BBU..11
[M]Lymphangioma NOS	BBU0.00
[M]Lymphangiosarcoma	BBU1.00
[M]Capillary lymphangioma	BBU2.00
[M]Cavernous lymphangioma	BBU3.00
[M]Cystic lymphangioma	BBU4.00
[M]Cystic hygroma	BBU4.11
[M]Hygroma	BBU4.12
[M]Lymphangiomyoma	BBU5.00
[M]Lymphangiomyomatosis	BBU6.00
[M]Haemolymphangioma	BBU7.00
[M]Lymphatic vessel tumour NOS	BBUz.00
[M]Osteomas and osteosarcomas	BBV..00
[M]Juxtacortical osteogenic sarcoma	BBV..11
[M]Parosteal osteosarcoma	BBV..12
[M]Periosteal osteogenic sarcoma	BBV..13
[M]Chondromatous neoplasms	BBW..00
[M]Osteochondroma	BBW0.00
[M]Cartilaginous exostosis	BBW0.11
[M]Ecchondroma	BBW0.12
[M]Osteocartilaginous exostosis	BBW0.13
[M]Osteochondromatosis NOS	BBW1.00
[M]Ecchondrosis	BBW1.11
[M]Chondroma NOS	BBW2.00
[M]Enchondroma	BBW2.11

[M]Chondromatosis NOS	BBW3.00
[M]Chondrosarcoma NOS	BBW4.00
[M]Fibrochondrosarcoma	BBW4.11
[M]Juxtacortical chondroma	BBW5.00
[M]Periosteal chondroma	BBW5.11
[M]Juxtacortical chondrosarcoma	BBW6.00
[M]Chondroblastoma NOS	BBW7.00
[M]Chondromatous giant cell tumour	BBW7.11
[M]Codman's tumour	BBW7.12
[M]Chondroblastoma, malignant	BBW8.00
[M]Mesenchymal chondrosarcoma	BBW9.00
[M]Chondromyxoid fibroma	BBWA.00
[M]Chondromatous neoplasm NOS	BBWz.00
[M]Giant cell tumours	BBX..00
[M]Giant cell tumour of bone NOS	BBX0.00
[M]Osteoclastoma	BBX0.11
[M]Giant cell tumour of bone, malignant	BBX1.00
[M]Giant cell bone sarcoma	BBX1.11
[M]Osteoclastoma, malignant	BBX1.12
[M]Giant cell tumour of soft parts NOS	BBX2.00
[M]Malignant giant cell tumour of soft parts	BBX3.00
[M]Giant cell tumour NOS	BBXz.00
[M]Miscellaneous bone tumours	BBY..00
[M]Ewing's sarcoma	BBY0.00
[M]Endothelial bone sarcoma	BBY0.11
[M]Adamantinoma of long bones	BBY1.00
[M]Tibial adamantinoma	BBY1.11
[M]Ossifying fibroma	BBY2.00
[M]Ossifying fibroma	BBY2.11
[M]Osteofibroma	BBY2.12
[M]Miscellaneous bone tumour NOS	BBYz.00
[M]Odontogenic tumours	BBZ..00
[M]Odontogenic tumour, benign	BBZ0.00
[M]Odontogenic tumour NOS	BBZ1.00
[M]Odontogenic tumour, malignant	BBZ2.00
[M]Intraosseous carcinoma	BBZ2.11
[M]Dentinoma	BBZ3.00
[M]Cementoma NOS	BBZ4.00
[M]Cementoblastoma, benign	BBZ5.00
[M]Cementifying fibroma	BBZ6.00
[M]Gigantiform cementoma	BBZ7.00
[M]Odontoma NOS	BBZ8.00
[M]Compound odontoma	BBZ9.00
[M]Complex odontoma	BBZA.00
[M]Ameloblastic fibro-odontoma	BBZB.00
[M]Ameloblastic odontosarcoma	BBZC.00

[M]Adenomatoid odontogenic tumour	BBZD.00
[M]Adenoameloblastoma	BBZD.11
[M]Calcifying odontogenic cyst	BBZE.00
[M]Ameloblastoma NOS	BBZF.00
[M]Adamantinoma NOS	BBZF.11
[M]Ameloblastoma, malignant	BBZG.00
[M]Adamantinoma, malignant	BBZG.11
[M]Odontoameloblastoma	BBZH.00
[M]Squamous odontogenic tumour	BBZJ.00
[M]Odontogenic myxoma	BBZK.00
[M]Odontogenic myxofibroma	BBZK.11
[M]Odontogenic fibroma NOS	BBZL.00
[M]Ameloblastic fibroma	BBZM.00
[M]Ameloblastic fibrosarcoma	BBZN.00
[M]Odontogenic fibrosarcoma	BBZN.11
[M]Calcifying epithelial odontogenic tumour	BBZP.00
[M]Odontogenic tumour NOS	BBZz.00
[M]Miscellaneous tumours	BBa..00
[M]Craniopharyngioma	BBa0.00
[M]Rathke's pouch tumour	BBa0.11
[M]Pinealoma	BBa1.00
[M]Pineocytoma	BBa2.00
[M]Pineoblastoma	BBa3.00
[M]Melanotic neuroectodermal tumour	BBa4.00
[M]Melanoameloblastoma	BBa4.11
[M]Melanotic progonoma	BBa4.12
[M]Retinal angle tumour	BBa4.13
[M]Chordoma	BBa5.00
[M]Miscellaneous tumour NOS	BBaz.00
[M]Gliomas	BBb..00
[M]Glioma, malignant	BBb0.00
[M]Glioma NOS	BBb0.11
[M]Gliosarcoma	BBb0.12
[M]Gliomatosis cerebri	BBb1.00
[M]Mixed glioma	BBb2.00
[M]Mixed glioma	BBb2.11
[M]Subependymal glioma	BBb3.00
[M]Subependymal astrocytoma NOS	BBb3.11
[M]Subependymal astrocytoma NOS	BBb3.12
[M]Subependymoma	BBb3.13
[M]Subependymal giant cell astrocytoma	BBb4.00
[M]Choroid plexus papilloma NOS	BBb5.00
[M]Choroid plexus papilloma, malignant	BBb6.00
[M]Ependymoma NOS	BBb7.00
[M]Ependymoma, anaplastic type	BBb8.00
[M]Ependymoblastoma	BBb8.11

[M]Papillary ependymoma	BBb9.00
[M]Myxopapillary ependymoma	BBbA.00
[M]Astrocytoma NOS	BBbB.00
[M]Astrocytic glioma	BBbB.11
[M]Astroganglioma	BBbB.12
[M]Astrocytoma, anaplastic type	BBbC.00
[M]Protoplasmic astrocytoma	BBbD.00
[M]Gemistocytic astrocytoma	BBbE.00
[M]Gemistocytoma	BBbE.11
[M]Fibrillary astrocytoma	BBbF.00
[M]Pilocytic astrocytoma	BBbG.00
[M]Juvenile astrocytoma	BBbG.11
[M]Piloid astrocytoma	BBbG.12
[M]Spongioblastoma NOS	BBbH.00
[M]Spongioblastoma polare	BBbJ.00
[M]Astroblastoma	BBbK.00
[M]Glioblastoma NOS	BBbL.00
[M]Glioblastoma multiforme	BBbL.11
[M]Spongioblastoma multiforme	BBbL.12
[M]Giant cell glioblastoma	BBbM.00
[M]Glioblastoma with sarcomatous component	BBbN.00
[M]Primitive polar spongioblastoma	BBbP.00
[M]Oligodendroglioma NOS	BBbQ.00
[M]Oligodendroglioma, anaplastic type	BBbR.00
[M]Oligodendroblastoma	BBbS.00
[M]Medulloblastoma NOS	BBbT.00
[M]Desmoplastic medulloblastoma	BBbU.00
[M]Medullomyoblastoma	BBbV.00
[M]Cerebellar sarcoma NOS	BBbW.00
[M]Monstrocellular sarcoma	BBbX.00
[M]Pleomorphic xanthoastrocytoma	BBbZ.00
[M]Primitive neuroectodermal tumour	BBba.00
[M]Glioma NOS	BBbz.00
[M]Neuroepitheliomatous neoplasms	BBc..00
[M]Ganglioneuromatous neoplasms	BBc0.00
[M]Neuroblastoma NOS	BBc1.00
[M]Sympathicoblastoma	BBc1.11
[M]Sympathicogonioma	BBc1.12
[M]Sympathogonioma	BBc1.13
[M]Medulloepithelioma NOS	BBc2.00
[M]Diktyoma	BBc2.11
[M]Teratoid medulloepithelioma	BBc3.00
[M]Neuroepithelioma NOS	BBc4.00
[M]Spongioneuroblastoma	BBc5.00
[M]Gangliоglioma	BBc6.00
[M]Glioneuroma	BBc6.11

[M]Neurocytoma	BBc7.00
[M]Neuroastrocytoma	BBc7.11
[M]Pacinian tumour	BBc8.00
[M]Retinoblastomas	BBc9.00
[M]Olfactory neurogenic tumour	BBcA.00
[M]Aesthesioneurocytoma	BBcB.00
[M]Aesthesioneuroblastoma	BBcC.00
[M]Olfactory neuroblastoma	BBcC.11
[M]Aesthesioneuroepithelioma	BBcD.00
[M]Olfactory neuroepithelioma	BBcD.11
[M]Neuroepitheliomatous neoplasm NOS	BBcz.00
[M]Meningiomas	BBd..00
[M]Nerve sheath tumour	BBe..00
[M]Neurofibromas	BBe..11
[M]Neurofibroma NOS	BBe0.00
[M]Neurofibromatosis NOS	BBe1.00
[M]Multiple neurofibromatosis	BBe1.11
[M]Von Recklinghausen's disease	BBe1.12
[M]Neurofibrosarcoma	BBe2.00
[M]Melanotic neurofibroma	BBe3.00
[M]Plexiform neurofibroma	BBe4.00
[M]Neurilemmoma NOS	BBe5.00
[M]Acoustic neuroma	BBe5.11
[M]Neurinoma	BBe5.12
[M]Schwannoma NOS	BBe5.13
[M]Neurinomatosis	BBe6.00
[M]Neurilemmoma, malignant	BBe7.00
[M]Schwannoma, malignant	BBe7.11
[M]Neuroma NOS	BBe8.00
[M]Triton tumour, malignant	BBe9.00
[M]Neurothekeoma	BBeA.00
[M]Nerve sheath tumour NOS	BBez.00
[M]Granular cell tumours and alveolar soft part sarcoma	BBf..00
[M]Granular cell tumour NOS	BBf0.00
[M]Granular cell tumour, malignant	BBf1.00
[M]Alveolar soft part sarcoma	BBf2.00
[M]Granular cell tumour or alveolar soft part sarcoma NOS	BBfz.00
Tumour of uterine body in pregnancy/childbirth/puerperium	L241.00
Uterine fibroids in pregnancy, childbirth and the puerperium	L241.11
Tumour of uterine body affecting obstetric care	L241000
Uterine fibroid affecting obstetric care	L241011
Tumour of uterine body - baby delivered	L241100
Uterine fibroid - baby delivered	L241111
Tumour of uterine body - baby delivered + p/n complication	L241200
Uterine fibroid - baby delivered + postpartum complication	L241211
Tumour of uterine body complicating a/n care, baby not deliv	L241300

Uterine fibroid complicating a/n care, baby not delivered	L241311
Tumour of uterine body complic p/n care, baby prev delivered	L241400
Uterine fibroid complicating p/n care - baby delivered prev	L241411
Uterine body tumour in pregnancy/childbirth/puerperium NOS	L241z00
Uterine fibroid in pregnancy/childbirth/puerperium NOS	L241z11
Polyp of cervix in pregnancy, childbirth and the puerperium	L246.11
Pelvic soft tissue abnormality in pregnancy/childbirth/puerp	L24z.00
Monostotic fibrous dysplasia	N332300
Fibrous cortical defect	N332400
Brown tumour of hyperparathyroidism	N332500

Table j-xiv Codes for Leukaemia

description	medcode
H/O: * leukaemia	1429
Suspected leukaemia	1J02.00
Plasma cell leukaemia	B631.00
Lymphoid leukaemia	B64..00
Lymphatic leukaemia	B64..11
Acute lymphoid leukaemia	B640.00
Chronic lymphoid leukaemia	B641.00
Chronic lymphatic leukaemia	B641.11
Subacute lymphoid leukaemia	B642.00
Other lymphoid leukaemia	B64y.00
Aleukaemic lymphoid leukaemia	B64y000
Prolymphocytic leukaemia	B64y100
Adult T-cell leukaemia	B64y200
Other lymphoid leukaemia NOS	B64yz00
Lymphoid leukaemia NOS	B64z.00
Myeloid leukaemia	B65..00
Acute myeloid leukaemia	B650.00
Chronic myeloid leukaemia	B651.00
Chronic granulocytic leukaemia	B651.11
Chronic eosinophilic leukaemia	B651000
Chronic neutrophilic leukaemia	B651200
Chronic myeloid leukaemia NOS	B651z00
Subacute myeloid leukaemia	B652.00
Other myeloid leukaemia	B65y.00
Aleukaemic myeloid leukaemia	B65y000
Acute promyelocytic leukaemia	B65y100
Other myeloid leukaemia NOS	B65yz00
Myeloid leukaemia NOS	B65z.00
Monocytic leukaemia	B66..00
Histiocytic leukaemia	B66..11
Monoblastic leukaemia	B66..12
Acute monocytic leukaemia	B660.00
Chronic monocytic leukaemia	B661.00
Subacute monocytic leukaemia	B662.00
Other monocytic leukaemia	B66y.00
Aleukaemic monocytic leukaemia	B66y000
Other monocytic leukaemia NOS	B66yz00
Monocytic leukaemia NOS	B66z.00
Other specified leukaemia	B67..00
Acute erythraemia and erythroleukaemia	B670.00
Megakaryocytic leukaemia	B672.00
Thrombocytic leukaemia	B672.11
Mast cell leukaemia	B673.00

Other and unspecified leukaemia	B67y.00
Lymphosarcoma cell leukaemia	B67y000
Other and unspecified leukaemia NOS	B67yz00
Other specified leukaemia NOS	B67z.00
Leukaemia of unspecified cell type	B68..00
Acute leukaemia NOS	B680.00
Chronic leukaemia NOS	B681.00
Subacute leukaemia NOS	B682.00
Other leukaemia of unspecified cell type	B68y.00
Leukaemia NOS	B68z.00
Myelomonocytic leukaemia	B69..00
Acute myelomonocytic leukaemia	B690.00
Chronic myelomonocytic leukaemia	B691.00
Subacute myelomonocytic leukaemia	B692.00
[M]Leukaemias	BBr..00
[M]Leukaemias unspecified	BBr0.00
[M]Leukaemia NOS	BBr0000
[M]Acute leukaemia NOS	BBr0100
[M]Blast cell leukaemia	BBr0111
[M]Blastic leukaemia	BBr0112
[M]Stem cell leukaemia	BBr0113
[M]Subacute leukaemia NOS	BBr0200
[M]Chronic leukaemia NOS	BBr0300
[M]Aleukaemic leukaemia NOS	BBr0400
[M]Leukaemia unspecified, NOS	BBr0z00
[M]Compound leukaemias	BBr1.00
[M]Compound leukaemia	BBr1000
[M]Mixed leukaemia	BBr1011
[M]Compound leukaemia NOS	BBr1z00
[M]Lymphoid leukaemias	BBr2.00
[M]Lymphoid leukaemia NOS	BBr2000
[M]Lymphatic leukaemia	BBr2011
[M]Acute lymphoid leukaemia	BBr2100
[M]Subacute lymphoid leukaemia	BBr2200
[M]Chronic lymphoid leukaemia	BBr2300
[M]Aleukaemic lymphoid leukaemia	BBr2400
[M]Prolymphocytic leukaemia	BBr2500
[M]Burkitt's cell leukaemia	BBr2600
[M]Adult T-cell leukaemia/lymphoma	BBr2700
[M]Other lymphoid leukaemia NOS	BBr2z00
[M]Plasma cell leukaemias	BBr3.00
[M]Plasma cell leukaemia	BBr3000
[M]Plasma cell leukaemia NOS	BBr3z00
[M]Erythroleukaemias	BBr4.00
[M]Erythroleukaemia	BBr4000
[M]Erythraemic myelosis	BBr4011

[M]Di Guglielmo's disease	BBr4111
[M]Chronic erythraemia	BBr4200
[M]Erythroleukaemia NOS	BBr4z00
[M]Lymphosarcoma cell leukaemias	BBr5.00
[M]Lymphosarcoma cell leukaemia	BBr5000
[M]Lymphosarcoma cell leukaemia NOS	BBr5z00
[M]Myeloid leukaemias	BBr6.00
[M]Myeloid leukaemia NOS	BBr6000
[M]Granulocytic leukaemia NOS	BBr6011
[M]Acute myeloid leukaemia	BBr6100
[M]Subacute myeloid leukaemia	BBr6200
[M]Chronic myeloid leukaemia	BBr6300
[M]Naegeli-type monocytic leukaemia	BBr6311
[M]Aleukaemic myeloid leukaemia	BBr6400
[M]Neutrophilic leukaemia	BBr6500
[M]Acute promyelocytic leukaemia	BBr6600
[M]Acute myelomonocytic leukaemia	BBr6700
[M]Chronic myelomonocytic leukaemia	BBr6800
[M]Other myeloid leukaemia NOS	BBr6z00
[M]Basophilic leukaemias	BBr7.00
[M]Basophilic leukaemia	BBr7000
[M]Basophilic leukaemia NOS	BBr7z00
[M]Eosinophilic leukaemias	BBr8.00
[M]Eosinophilic leukaemia	BBr8000
[M]Eosinophilic leukaemia NOS	BBr8z00
[M]Monocytic leukaemias	BBr9.00
[M]Monocytic leukaemia NOS	BBr9000
[M]Histiocytic leukaemia	BBr9011
[M]Schilling-type monocytic leukaemia	BBr9012
[M]Acute monocytic leukaemia	BBr9100
[M]Subacute monocytic leukaemia	BBr9200
[M]Chronic monocytic leukaemia	BBr9300
[M]Aleukaemic monocytic leukaemia	BBr9400
[M]Other monocytic leukaemia NOS	BBr9z00
[M]Miscellaneous leukaemias	BBrA.00
[M]Mast cell leukaemia	BBrA000
[M]Megakaryocytic leukaemia	BBrA100
[M]Thrombocytic leukaemia	BBrA111
[M]Hairy cell leukaemia	BBrA400
[M]Leukaemic reticuloendotheliosis	BBrA411
[M]Acute megakaryoblastic leukaemia	BBrA500
[M]Leukaemic reticuloendotheliosis	BBrA800
[M]Miscellaneous leukaemia NOS	BBrAz00
[M]Leukaemia NOS	BBrz.00
[X]Other lymphoid leukaemia	ByuD500
[X]Other myeloid leukaemia	ByuD600

[X]Other monocytic leukaemia	ByuD700
[X]Other specified leukaemias	ByuD800
[X]Other leukaemia of unspecified cell type	ByuD900
[V]Personal history of leukaemia	ZV10600
[V]Personal history of lymphoid leukaemia	ZV10611
[V]Personal history of monocytic leukaemia	ZV10612
[V]Personal history of myeloid leukaemia	ZV10613

Table j-xv Codes for Lymphoma

description	medcode
Lymphoma stage I	4M20.00
Lymphoma stage II	4M21.00
Lymphoma stage III	4M22.00
Lymphoma stage IV	4M23.00
HIV disease resulting in Burkitt's lymphoma	A789600
HIV dis resulting oth types of non-Hodgkin's lymphoma	A789700
[X]HIV disease resulting in other non-Hodgkin's lymphoma	AyuC600
Lymphosarcoma	B601.00
Burkitt's lymphoma	B602.00
Burkitt's lymphoma of unspecified site	B602000
Burkitt's lymphoma of lymph nodes of head, face and neck	B602100
Burkitt's lymphoma of intrathoracic lymph nodes	B602200
Burkitt's lymphoma of intra-abdominal lymph nodes	B602300
Burkitt's lymphoma of lymph nodes of axilla and upper limb	B602400
Burkitt's lymphoma of lymph nodes of inguinal region and leg	B602500
Burkitt's lymphoma of intrapelvic lymph nodes	B602600
Burkitt's lymphoma of spleen	B602700
Burkitt's lymphoma of lymph nodes of multiple sites	B602800
Burkitt's lymphoma NOS	B602z00
Other specified reticulosarcoma or lymphosarcoma	B60y.00
Reticulosarcoma or lymphosarcoma NOS	B60z.00
Nodular lymphoma (Brill - Symmers disease)	B620.00
Reticulosarcoma - follicular or nodular	B620.11
Nodular lymphoma of unspecified site	B620000
Nodular lymphoma of lymph nodes of head, face and neck	B620100
Nodular lymphoma of intrathoracic lymph nodes	B620200
Nodular lymphoma of intra-abdominal lymph nodes	B620300
Nodular lymphoma of lymph nodes of axilla and upper limb	B620400
Nodular lymphoma of lymph nodes of inguinal region and leg	B620500
Nodular lymphoma of intrapelvic lymph nodes	B620600
Nodular lymphoma of spleen	B620700
Nodular lymphoma of lymph nodes of multiple sites	B620800
Nodular lymphoma NOS	B620z00
Mycosis fungoides	B621.00
Sezary's disease	B622.00
Malignant histiocytosis	B623.00
Malignant histiocytosis of unspecified site	B623000
Malignant histiocytosis of lymph nodes head, face and neck	B623100
Malignant histiocytosis of intrathoracic lymph nodes	B623200
Malignant histiocytosis of intra-abdominal lymph nodes	B623300
Malignant histiocytosis of lymph nodes of axilla and arm	B623400
Malignant histiocytosis of lymph nodes inguinal and leg	B623500
Malignant histiocytosis of intrapelvic lymph nodes	B623600

Malignant histiocytosis of spleen	B623700
Malignant histiocytosis of lymph nodes of multiple sites	B623800
Malignant histiocytosis NOS	B623z00
Leukaemic reticuloendotheliosis	B624.00
Leukaemic reticuloendotheliosis	B624.11
Letterer-Siwe disease	B625.00
Histiocytosis X (acute, progressive)	B625.11
Malignant mast cell tumours	B626.00
Mast cell malignancy of unspecified site	B626000
Mast cell malignancy of lymph nodes of head, face and neck	B626100
Mast cell malignancy of intrathoracic lymph nodes	B626200
Mast cell malignancy of intra-abdominal lymph nodes	B626300
Mast cell malignancy of lymph nodes of axilla and upper limb	B626400
Mast cell malignancy of lymph nodes inguinal region and leg	B626500
Mast cell malignancy of intrapelvic lymph nodes	B626600
Mast cell malignancy of spleen	B626700
Mast cell malignancy of lymph nodes of multiple sites	B626800
Malignant mast cell tumour NOS	B626z00
Non - Hodgkin's lymphoma	B627.00
Follicular non-Hodgkin's small cleaved cell lymphoma	B627000
Follicular non-Hodg mixed sml cleavd & lge cell lymphoma	B627100
Follicular non-Hodgkin's large cell lymphoma	B627200
Diffuse non-Hodgkin's small cell (diffuse) lymphoma	B627300
Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma	B627400
Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma	B627500
Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma	B627600
Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma	B627700
Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)	B627800
Other types of follicular non-Hodgkin's lymphoma	B627B00
Follicular non-Hodgkin's lymphoma	B627C00
Follicular lymphoma NOS	B627C11
Diffuse non-Hodgkin's centroblastic lymphoma	B627D00
Unspecified B-cell non-Hodgkin's lymphoma	B627W00
Diffuse non-Hodgkin's lymphoma, unspecified	B627X00
Malignant lymphoma otherwise specified	B62x.00
T-zone lymphoma	B62x000
Lymphoepithelioid lymphoma	B62x100
Peripheral T-cell lymphoma	B62x200
Malignant reticuloendotheliosis	B62x300
Malignant reticulosis	B62x400
True histiocytic lymphoma	B62x600
Oth and unspecif peripheral & cutaneous T-cell lymphomas	B62xX00
Malignant lymphoma NOS	B62y.00
Malignant lymphoma NOS of unspecified site	B62y000
Malignant lymphoma NOS of lymph nodes of head, face and neck	B62y100
Malignant lymphoma NOS of intrathoracic lymph nodes	B62y200

Malignant lymphoma NOS of intra-abdominal lymph nodes	B62y300
Malignant lymphoma NOS of lymph nodes of axilla and arm	B62y400
Malignant lymphoma NOS of lymph node inguinal region and leg	B62y500
Malignant lymphoma NOS of intrapelvic lymph nodes	B62y600
Malignant lymphoma NOS of spleen	B62y700
Malignant lymphoma NOS of lymph nodes of multiple sites	B62y800
Malignant lymphoma NOS	B62yz00
Malignant neoplasms of lymphoid and histiocytic tissue NOS	B62z.00
Chloroma	B653000
Neoplasm of uncertain behaviour of histiocytic and mast cell	B935.00
Histiocytic tumour NOS	B935.11
Mastocytoma NOS	B935.12
Neoplasm of uncertain behaviour of plasma cells	B936.00
Myeloma - solitary	B936.11
Plasmacytoma NOS	B936.12
Neop uncertain behaviour other lymphatic/haematopoietic tiss	B937.00
[M]Adenolymphoma	BBB1.00
[M]Lymphatic vessel tumours	BBU..00
[M]Lymphangiomatous tumours	BBU..11
[M]Lymphomas, NOS or diffuse	BBg..00
[M]Lymphomatous tumour, benign	BBg0.00
[M]Malignant lymphoma NOS	BBg1.00
[M]Lymphoma NOS	BBg1.11
[M]Malignant lymphoma, diffuse NOS	BBg1000
[M]Malignant lymphoma, non Hodgkin's type	BBg2.00
[M]Non Hodgkins lymphoma	BBg2.11
[M]Malignant lymphoma, undifferentiated cell type NOS	BBg3.00
[M]Malignant lymphoma, stem cell type	BBg4.00
[M]Malignant lymphoma, convoluted cell type NOS	BBg5.00
[M]Lymphosarcoma NOS	BBg6.00
[M]Malignant lymphoma, lymphoplasmacytoid type	BBg7.00
[M]Malignant lymphoma, immunoblastic type	BBg8.00
[M]Malignant lymphoma, mixed lymphocytic-histiocytic NOS	BBg9.00
[M]Reticulolymphosarcoma NOS	BBg9.11
[M]Reticulolymphosarcoma, diffuse	BBg9.12
[M]Malignant lymphoma, centroblastic-centrocytic, diffuse	BBgA.00
[M]Germinoblastoma, diffuse	BBgA.11
[M]Malignant lymphoma, follicular centre cell NOS	BBgB.00
[M]Malignant lymphoma, lymphocytic, well differentiated NOS	BBgC.00
[M]Lymphocytic lymphoma NOS	BBgC.11
[M]Lymphocytic lymphosarcoma NOS	BBgC.12
[M]Malig lymphoma, lymphocytic, intermediate different NOS	BBgD.00
[M]Malignant lymphoma, centrocytic	BBgE.00
[M]Malignant lymphoma, follicular centre cell, cleaved NOS	BBgF.00
[M]Malignant lymphoma, lymphocytic, poorly different NOS	BBgG.00
[M]Lymphoblastic lymphosarcoma NOS	BBgG.11

[M]Lymphoblastic lymphoma NOS	BBgG.12
[M]Lymphoblastoma NOS	BBgG.13
[M]Prolymphocytic lymphosarcoma	BBgH.00
[M]Malignant lymphoma, centroblastic type NOS	BBgJ.00
[M]Germinoblastic sarcoma NOS	BBgJ.11
[M]Malig lymphoma, follicular centre cell, non-cleaved NOS	BBgK.00
[M]Malignant lymphoma, small lymphocytic NOS	BBgL.00
[M]Malignant lymphoma, small cleaved cell, diffuse	BBgM.00
[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse	BBgN.00
[M]Malignant lymphoma, mixed small and large cell, diffuse	BBgP.00
[M]Malignant lymphomatous polyposis	BBgQ.00
[M]Malignant lymphoma, large cell, diffuse NOS	BBgR.00
[M]Malignant lymphoma, large cell, cleaved, diffuse	BBgS.00
[M]Malignant lymphoma, large cell, noncleaved, diffuse	BBgT.00
[M]Malignant lymphoma, small cell, noncleaved, diffuse	BBgV.00
[M]Lymphoma, diffuse or NOS	BBgz.00
[M]Reticulosarcomas	BBh..00
[M]Hodgkin's disease	BBj..00
[M]Lymphomas, nodular or follicular	BBk..00
[M]Malignant lymphoma, nodular NOS	BBk0.00
[M]Brill - Symmers' disease	BBk0.11
[M]Follicular lymphosarcoma NOS	BBk0.12
[M]Giant follicular lymphoma	BBk0.13
[M]Nodular lymphosarcoma NOS	BBk0.14
[M]Malig lymphoma, mixed lymphocytic-histiocytic, nodular	BBk1.00
[M]Reticulolymphosarcoma, follicular	BBk1.11
[M]Reticulolymphosarcoma, nodular	BBk1.12
[M]Malignant lymphoma, centroblastic-centrocytic, follicular	BBk2.00
[M]Germinoblastoma, follicular	BBk2.11
[M]Malig lymphoma, lymphocytic, well differentiated,nodular	BBk3.00
[M]Malig lymp, lymphocytic, intermediate different, nodular	BBk4.00
[M]Malig lymp, follicular centre cell, cleaved, follicular	BBk5.00
[M]Malig lymp, lymphocytic, poorly differentiated, nodular	BBk6.00
[M]Malignant lymphoma, centroblastic type, follicular	BBk7.00
[M]Germinoblastic sarcoma, follicular	BBk7.11
[M]Malig lymp,follicular centre cell,noncleaved,follicular	BBk8.00
[M]Lymphoma, nodular or follicular NOS	BBkz.00
[M]Mycosis fungoides	BBl..00
[M]Miscellaneous reticuloendothelial neoplasms	BBm..00
[M]Malignant histiocytosis	BBm1.00
[M]Letterer - Siwe disease	BBm3.00
[M]Acute progressive histiocytosis X	BBm3.12
[M]True histiocytic lymphoma	BBm4.00
[M] Peripheral T-cell lymphoma NOS	BBm5.00
[M] Monocytoid B-cell lymphoma	BBm9.00
[M] Cutaneous lymphoma	BBmD.00

[M] Large cell lymphoma	BBmH.00
[M]Waldenstrom's macroglobulinaemia	BBmK.00
[M]Miscellaneous reticuloendothelial neoplasm NOS	BBmz.00
[M]Plasma cell tumours	BBn..00
[M]Plasma cell myeloma	BBn0.00
[M]Multiple myeloma	BBn0.11
[M]Myeloma NOS	BBn0.12
[M]Myelomatosis	BBn0.13
[M]Plasmacytic myeloma	BBn0.14
[M]Plasma cell tumour, benign	BBn1.00
[M]Plasmacytoma, benign	BBn1.11
[M]Plasmacytoma NOS	BBn2.00
[M]Monostotic myeloma	BBn2.11
[M]Solitary myeloma	BBn2.12
[M]Plasma cell tumour, malignant	BBn3.00
[M]Plasma cell tumour NOS	BBnz.00
[M]Mast cell tumours	BBp..00
[M]Mastocytoma NOS	BBp0.00
[M]Mast cell sarcoma	BBp1.00
[M]Malignant mastocytosis	BBp2.00
[M]Mast cell tumour NOS	BBpz.00
[M]Burkitt's tumours	BBq..00
[M]Burkitt's tumour	BBq0.00
[M]Burkitt's tumour NOS	BBqz.00
[M]Leukaemias	BBr..00
[M]Other lymphoid leukaemia NOS	BBr2z00
[M]Chloroma	BBrA311
[M]Misc myeloproliferative and lymphoproliferative disorders	BBs..00
[M]Monocytoid B-cell lymphoma	BBv0.00
[M]AngiocentricT-cell lymphoma	BBv2.00
[X]Other Hodgkin's disease	ByuD000
[X]Other types of follicular non-Hodgkin's lymphoma	ByuD100
[X]Other types of diffuse non-Hodgkin's lymphoma	ByuD200
[X]Other specified types of non-Hodgkin's lymphoma	ByuD300
[X]Other malignant immunoproliferative diseases	ByuD400
[X]Oth spcf mal neoplsm/lymphoid,haematopoietic+rltd tissue	ByuDA00
[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf	ByuDB00
[X]Diffuse non-Hodgkin's lymphoma, unspecified	ByuDC00
[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas	ByuDD00
[X]Unspecified B-cell non-Hodgkin's lymphoma	ByuDE00
[X]Non-Hodgkin's lymphoma, unspecified type	ByuDF00
[X]Non-Hodgkin's lymphoma NOS	ByuDF11
Histiocytosis X , chronic	C37y500
Histiocytosis X , unspecified	C37y600
Histiocytosis, unspecified	C37y700
Haemophagocytic lymphohistiocytosis	C37y800

Langerhans' cell histiocytosis	C37yB00
Histiocytosis X (chronic)	C37yz11
Lipochrome histiocytosis - familial	D401.12
Familial erythrophagocytic lymph histiocytosis	D401100
FEL-Familial erythrophagocytic lymph histiocytosis	D401111
[X]Other histiocytosis syndromes	Dyu4400

Table j-xvi Codes for Metastatic solid tumour

description	medcode
Pain from metastases	1D18.00
Secondary malignant neoplasm of liver	B153.00
Secondary and unspecified malignant neoplasm of lymph nodes	B56..00
Lymph node metastases	B56..11
Secondary and unspec malig neop lymph nodes head/face/neck	B560.00
Secondary and unspec malig neop of superficial parotid LN	B560000
Secondary and unspec malignant neoplasm mastoid lymph nodes	B560100
Secondary and unspec malig neop superficial cervical LN	B560200
Secondary and unspec malignant neoplasm occipital lymph node	B560300
Secondary and unspec malig neop deep parotid lymph nodes	B560400
Secondary and unspec malig neop submandibular lymph nodes	B560500
Secondary and unspec malig neop of facial lymph nodes	B560600
Secondary and unspec malig neop submental lymph nodes	B560700
Secondary and unspec malig neop anterior cervical LN	B560800
Secondary and unspec malig neop deep cervical LN	B560900
Secondary unspec malig neop lymph nodes head/face/neck NOS	B560z00
Secondary and unspec malig neop intrathoracic lymph nodes	B561.00
Secondary and unspec malig neop internal mammary lymph nodes	B561000
Secondary and unspec malig neop intercostal lymph nodes	B561100
Secondary and unspec malig neop diaphragmatic lymph nodes	B561200
Secondary and unspec malig neop ant mediastinal lymph nodes	B561300
Secondary and unspec malig neop post mediastinal lymph nodes	B561400
Secondary and unspec malig neop paratracheal lymph nodes	B561500
Secondary and unspec malig neop superfic tracheobronchial LN	B561600
Secondary and unspec malig neop inferior tracheobronchial LN	B561700
Secondary and unspec malig neop bronchopulmonary lymph nodes	B561800
Secondary and unspec malig neop pulmonary lymph nodes	B561900
Secondary and unspec malig neop intrathoracic LN NOS	B561z00
Secondary and unspec malig neop intra-abdominal lymph nodes	B562.00
Secondary and unspec malig neop coeliac lymph nodes	B562000
Secondary and unspec malig neop superficial mesenteric LN	B562100
Secondary and unspec malig neop inferior mesenteric LN	B562200
Secondary and unspec malig neop common iliac lymph nodes	B562300
Secondary and unspec malig neop external iliac lymph nodes	B562400
Secondary and unspec malig neop intra-abdominal LN NOS	B562z00
Secondary and unspec malig neop axilla and upper limb LN	B563.00
Secondary and unspec malig neop axillary lymph nodes	B563000
Secondary and unspec malig neop supratrochlear lymph nodes	B563100
Secondary and unspec malig neop infraclavicular lymph nodes	B563200
Secondary and unspec malig neop pectoral lymph nodes	B563300
Secondary and unspec malig neop axilla and upper limb LN NOS	B563z00
Secondary and unspec malig neop inguinal and lower limb LN	B564.00
Secondary and unspec malig neop superficial inguinal LN	B564000

Secondary and unspec malig neop deep inguinal lymph nodes	B564100
Secondary and unspec malig neop popliteal lymph nodes	B564200
Secondary and unspec malig neop of inguinal and leg LN NOS	B564z00
Secondary and unspec malig neop intrapelvic lymph nodes	B565.00
Secondary and unspec malig neop internal iliac lymph nodes	B565000
Secondary and unspec malig neop inferior epigastric LN	B565100
Secondary and unspec malig neop circumflex iliac LN	B565200
Secondary and unspec malig neop sacral lymph nodes	B565300
Secondary and unspec malig neop obturator lymph nodes	B565400
Secondary and unspec malig neop intrapelvic LN NOS	B565z00
Secondary and unspec malig neop lymph nodes multiple sites	B56y.00
Secondary and unspec malig neop lymph nodes NOS	B56z.00
Secondary malig neop of respiratory and digestive systems	B57..00
Metastases of respiratory and/or digestive systems	B57..11
Secondary carcinoma of respiratory and/or digestive systems	B57..12
Secondary malignant neoplasm of lung	B570.00
Secondary malignant neoplasm of mediastinum	B571.00
Secondary malignant neoplasm of pleura	B572.00
Secondary malignant neoplasm of other respiratory organs	B573.00
Secondary malignant neoplasm of small intestine and duodenum	B574.00
Secondary malignant neoplasm of duodenum	B574000
Secondary malignant neoplasm of jejunum	B574100
Secondary malignant neoplasm of ileum	B574200
Secondary malig neop of small intestine or duodenum NOS	B574z00
Secondary malignant neoplasm of large intestine and rectum	B575.00
Secondary malignant neoplasm of colon	B575000
Secondary malignant neoplasm of rectum	B575100
Secondary malig neop of large intestine or rectum NOS	B575z00
Secondary malig neop of retroperitoneum and peritoneum	B576.00
Secondary malignant neoplasm of retroperitoneum	B576000
Secondary malignant neoplasm of peritoneum	B576100
Secondary malig neop of retroperitoneum or peritoneum NOS	B576z00
Secondary malignant neoplasm of liver	B577.00
Liver metastases	B577.11
Secondary malignant neoplasm of other digestive organ	B57y.00
Secondary malig neop of respiratory or digestive system NOS	B57z.00
Secondary malignant neoplasm of other specified sites	B58..00
Secondary carcinoma of other specified sites	B58..11
Secondary malignant neoplasm of kidney	B580.00
Secondary malignant neoplasm of other urinary organs	B581.00
Secondary malignant neoplasm of ureter	B581000
Secondary malignant neoplasm of bladder	B581100
Secondary malignant neoplasm of urethra	B581200
Secondary malignant neoplasm of other urinary organ NOS	B581z00
Secondary malignant neoplasm of skin	B582.00
Secondary malignant neoplasm of skin of head	B582000

Secondary malignant neoplasm of skin of face	B582100
Secondary malignant neoplasm of skin of neck	B582200
Secondary malignant neoplasm of skin of trunk	B582300
Secondary malignant neoplasm of skin of shoulder and arm	B582400
Secondary malignant neoplasm of skin of hip and leg	B582500
Secondary malignant neoplasm of skin of breast	B582600
Secondary malignant neoplasm of skin NOS	B582z00
Secondary malignant neoplasm of brain and spinal cord	B583.00
Secondary malignant neoplasm of brain	B583000
Secondary malignant neoplasm of spinal cord	B583100
Cerebral metastasis	B583200
Secondary malignant neoplasm of brain or spinal cord NOS	B583z00
Secondary malignant neoplasm of other part of nervous system	B584.00
Secondary malignant neoplasm of bone and bone marrow	B585.00
Pathological fracture due to metastatic bone disease	B585000
Secondary malignant neoplasm of ovary	B586.00
Secondary malignant neoplasm of adrenal gland	B587.00
Secondary malignant neoplasm of other specified sites	B58y.00
Secondary malignant neoplasm of breast	B58y000
Secondary malignant neoplasm of uterus	B58y100
Secondary malignant neoplasm of cervix uteri	B58y200
Secondary cancer of the cervix	B58y211
Secondary malignant neoplasm of vagina	B58y300
Secondary malignant neoplasm of vulva	B58y400
Secondary cancer of the vulva	B58y411
Secondary malignant neoplasm of prostate	B58y500
Secondary malignant neoplasm of testis	B58y600
Secondary malignant neoplasm of penis	B58y700
Secondary malignant neoplasm of epididymis and vas deferens	B58y800
Secondary malignant neoplasm of tongue	B58y900
Secondary malignant neoplasm of other specified site NOS	B58yz00
Secondary malignant neoplasm of other specified site NOS	B58z.00
Secondary malignant neoplasm of unknown site	B594.00
[M]Neoplasm, metastatic	BB03.00
[M]Secondary neoplasm	BB03.11
[M]Neoplasm, malig, uncertain whether primary or metastatic	BB04.00
[M]Carcinoma, metastatic, NOS	BB13.00
[M]Secondary carcinoma	BB13.11
[M]Squamous cell carcinoma, metastatic NOS	BB2B.00
[M]Adenocarcinoma, metastatic, NOS	BB53.00
[M]Metastatic signet ring cell carcinoma	BB85100
[M]No microscopic confirmation tumour, clinically metastatic	BBy2.00
[X]Malignant neoplasm of ill-defined, secondary and unspeci	ByuC.00
[X]Secondary malignant neoplasm/oth+unspc respiratory organs	ByuC300
[X]Secondary malignant neoplasm/oth+unspcfd digestive organs	ByuC400
[X]Secondary malignant neoplasm of other specified sites	ByuC700

Table j-xvii Codes for AIDS

description	medcode
HIV positive	43C3.11
AIDS carrier	65QA.00
Notification of AIDS	65VE.00
Acute human immunodeficiency virus infection	A788000
Asymptomatic human immunodeficiency virus infection	A788100
HIV infection with persistent generalised lymphadenopathy	A788200
Human immunodeficiency virus with constitutional disease	A788300
Human immunodeficiency virus with neurological disease	A788400
Human immunodeficiency virus with secondary infection	A788500
Human immunodeficiency virus with secondary cancers	A788600
HIV disease result/haematological+immunologic abnorms,NEC	A788U00
HIV disease resulting in multiple diseases CE	A788V00
HIV disease resulting in unspecified malignant neoplasm	A788W00
HIV disease resulting/unspcf infectious+parasitic disease	A788X00
Human immunodeficiency virus with other clinical findings	A788y00
Acquired human immunodeficiency virus infection syndrome NOS	A788z00
HIV disease resulting in mycobacterial infection	A789000
HIV disease resulting in cytomegaloviral disease	A789100
HIV disease resulting in candidiasis	A789200
HIV disease resulting in Pneumocystis carinii pneumonia	A789300
HIV disease resulting in multiple infections	A789400
HIV disease resulting in Kaposi's sarcoma	A789500
HIV disease resulting in Burkitt's lymphoma	A789600
HIV dis resulting oth types of non-Hodgkin's lymphoma	A789700
HIV disease resulting in multiple malignant neoplasms	A789800
HIV disease resulting in lymphoid interstitial pneumonitis	A789900
HIV disease resulting in wasting syndrome	A789A00
HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu	A789X00
[X]HIV disease resulting in other bacterial infections	AyuC000
[X]HIV disease resulting in other viral infections	AyuC100
[X]HIV disease resulting in other mycoses	AyuC200
[X]HIV disease resulting in multiple infections	AyuC300
[X]HIV disease resulting/other infectious+parasitic diseases	AyuC400
[X]HIV disease resulting/unspcf infectious+parasitic disease	AyuC500
[X]HIV disease resulting in other non-Hodgkin's lymphoma	AyuC600
[X]HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu	AyuC700
[X]HIV disease resulting in other malignant neoplasms	AyuC800
[X]HIV disease resulting in unspecified malignant neoplasm	AyuC900
[X]HIV disease resulting in multiple diseases CE	AyuCA00
[X]HIV disease result/haematological+immunologic abnorms,NEC	AyuCB00
[X]HIV disease resulting in other specified conditions	AyuCC00
[X]Unspecified human immunodeficiency virus [HIV] disease	AyuCD00

[X]Dementia in human immunodef virus [HIV] disease	Eu02400
[D]Laboratory evidence of human immunodefiency virus [HIV]	R109.00

Appendix III-k Codes for liver transplant

Description	medcode
Transplantation of liver	7800
Orthotopic transplantation of liver	7800000
Heterotopic transplantation of liver	7800100
Auxillary liver transplant	7800111
Piggy back liver transplant	7800112
Replacement of previous liver transplant	7800200
Other specified transplantation of liver	7800y00
Transplantation of liver NOS	7800z00
TRANSPLANTATION LIVER	K5005
Liver transplant failure and rejection	SP08600
Liver transplant with complication, without blame	TB00200
[V]Liver transplanted	ZV42700