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Highlights

- Both all-cause and epilepsy-related mortality decreased significantly during the pandemic in this cohort of epilepsy patients.
- A shift to telemedicine saw provision of epilepsy specialist services maintained despite an overall reduction in outpatient hospital services.
- The proportion of epilepsy patients receiving treatment for mental health conditions has increased over time.

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The impact of the COVID-19 pandemic on a cohort of adults with epilepsy

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Abstract

Objectives

The aim of this study was to assess the direct and indirect impacts of the COVID-19 pandemic on adults with epilepsy in Glasgow.

Methods

We used routinely collected data for a previously identified cohort of patients with epilepsy to evaluate access to scheduled and unscheduled care with quarterly rates of inpatient admissions, outpatient attendance and accident & emergency attendance calculated. Anti-seizure medication prescribing and persistence, incidence of anxiety and depression and deaths for a cohort of patients with epilepsy was evaluated prior to the pandemic in comparison to during the pandemic, from 2015 to 2021.

Results

All-cause mortality and epilepsy related mortality showed a statistically significant reduction during the pandemic. Although overall rates of out-patient hospital attendance dropped during the early stages of the pandemic (and had not returned to pre-pandemic levels by the end of 2021) epilepsy-related services saw a maintenance of patient contact as a result of a rapid adoption of telephone clinics. A significant decrease in overall mortality was observed in PWE during the pandemic compared to the pre-pandemic period. COVID-19 was the single commonest cause of death in PWE during the pandemic (61/453) and 160 patients (3.7%) had at least 1 admission to hospital for COVID-19. Anti-seizure medication (ASM) prescribing rates remained stable during the pandemic. During the pandemic an average of 38.8% of cohort patients were treated for depression and 16.3% for anxiety per quarter, 8.2% and 12.4% of whom had not been previously treated for these conditions respectively.

Conclusion

We have shown that during a national lockdown, in the context of a pandemic, mortality in patients with epilepsy has reduced, while out-patient services were delivered remotely, primarily via the telephone. The reasons for this remain unclear but suggest that some of the excess mortality in people with epilepsy may be potentially avoidable by changes in lifestyle.

Introduction

The COVID-19 pandemic has presented an unprecedented challenge to global public health, causing millions of deaths around the world, and potentially resulting in lasting health problems for some people who have survived infection. The first positive case of COVID-19 infection in Scotland was identified on 1st March 2020, with the first death of a patient with COVID-19 occurring on 13th March.(1) The rapid rise in infection rate and hospital admission resulted in a period of national lockdown which started on the 24th of March, with varying levels of restriction on day-to-day activities being in place over the following two years. In total between the first case and the end of 2021 there were 44,335 hospital admissions and 12,490 deaths involving COVID-19 in Scotland – an average of 457 and 130 per week respectively.(2)

There is a growing base of knowledge about the disease and its impact, and within the current literature there is no conclusive evidence to support a direct increased risk of COVID-19 infection in people with epilepsy nor is there conclusive evidence supporting a direct relationship between COVID-19 infection and increased seizure frequency.(3-6) However, several survey-based studies have highlighted other ways the pandemic has potentially impacted the lives of patients with epilepsy (PWE), including increased seizure frequency, increased prevalence of mental health issues including depression and anxiety, and concerns around reduced access to healthcare and medications.(5, 7-10) Additionally, people with epilepsy have a higher rate of comorbidity than the general population, and some of these conditions are associated with greater risk of mortality or serious infection from COVID-19 (including asthma, COPD and intellectual disabilities).(5, 11, 12) Due to the novel nature of COVID-19, there remains much to learn about its interactions with other conditions.

Beyond the direct impact of COVID-19 infection on people's health, there have also been wider impacts on health and social care provision due to the scale of the pandemic and societal and economic impacts from the restrictions used to limit the spread of the virus. Within NHS Greater Glasgow and Clyde (NHS GGC) a small number of clinics were initially suspended but all epilepsy clinics were re-instated and carried out remotely, most continuing as such at the time of writing. Understanding how these factors (and indeed how the national lockdown) impacted the lives of patients with chronic conditions such as epilepsy is an important step in learning lessons from the pandemic and in improving future care.

The aim of this study was to investigate direct and indirect impacts of the COVID-19 pandemic on a cohort of adults with epilepsy.

Methods

Study population

Individuals registered with a general practitioner in Scotland are assigned a unique, ten-digit Community Health Index (CHI) number which is appended to all records of healthcare encounters within NHS Scotland services. This allows the linkage of routinely collected data from across NHS services related to an individual. The study period ran from 01/01/2012 to 30/11/2021, with the pandemic period defined as the time from the start of the second quarter of 2020 and running through to the end of the study period. Patients were included in the cohort if they had at least one prescription for an anti-seizure medication (ASM) and one or more of the following: an epilepsy-related inpatient admission to hospital, an epilepsy-related A&E attendance or an outpatient neurology clinic attendance during the follow-up period. All patients in this study were registered with a GP within the NHS GGC health board area.⁽¹³⁾ Patients were excluded if they were younger than 16 years old, or if they had only ever been prescribed gabapentin monotherapy during the study period. Patients were followed up from the date of their first ASM prescription and censored at time of death or at the time they moved out of the NHS GGC health board area, identified through National Records Scotland death data and registration with an out of health board GP respectively. Data were accessed using the Glasgow Safe Haven platform⁽¹⁴⁾, and included demographic information, deaths, hospitalisations, A&E attendance, outpatient clinic attendance and prescriptions dispensed within the community.⁽¹⁵⁾

Definitions

Hospitalisations, A&E attendances, and deaths were defined as being epilepsy-related if there was an ICD-10 code for epilepsy (G40.x) in any position. Similarly, hospitalisations and deaths were identified based on the presence of a relevant ICD-10 code (U07.x) in the positions outlined in the Public Health Scotland ICD-10 analytical guidance.⁽¹⁶⁾ Quarterly death rates were calculated by dividing all cohort deaths, epilepsy-related deaths, and COVID-19 related deaths by the estimated annual population of the NHS Greater Glasgow and Clyde health board area according to National Records Scotland (NRS).⁽¹⁷⁾ Regression modelling was used to assess for significant differences between the rates of all-cause and epilepsy-related death during the pre-pandemic and pandemic periods. We used time series regression with ARMA errors.⁽¹⁸⁾ The form of the error model was derived from plots of the partial autocorrelation and autocorrelation functions. The resulting residuals were then tested for white noise using the Ljung-Box statistic.⁽¹⁹⁾ Structural breaks in the series were identified from the time series plots and included as either a step change or slope change. All models included a control for the underlying trend in the deaths series.

The proportion of total cohort patients who had at least one inpatient admission (for any reason, for epilepsy and for COVID-19), outpatient clinic attendance (at any clinic and neurology clinics only), A&E attendance (for any reason and for epilepsy) and at least 1 prescription dispensed for an ASM per quarter was calculated. Periods of persistent use of anti-seizure medications was inferred using an allowable gap of 90 days between individual prescriptions for any ASM, and patients were considered to have discontinued their medication if they exceeded this gap. Anti-seizure medications were defined as compounds appearing in sub-section 04.08.01 of the British National Formulary (BNF).

Comorbid mental health conditions were identified during the pre-pandemic and pandemic period using hospitalisation and dispensing records based on criteria used in previous studies.⁽²⁰⁾ Patients were considered to have been treated for depression or anxiety if they had at least 4 prescriptions for relevant medications (BNF section 04.03 for depression and BNF sub-sections 04.01.01 and 04.01.02 for anxiety) or at least 1 hospital admission with an relevant ICD-10 code (F32.x, F33.x, F20.4, F31.3 – F31.5, F41.2, F43.2 for depression and F064, F40.x, F41.x for anxiety). We also determined the proportion of patients who had at least 1 relevant record per quarter over the duration of follow-up.

All analyses were conducted in R 3.5.0 using RStudio v1.1.453 and Stata v 18.0.

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Results

Between January 2012 and November 2021, 6,459 patients met the criteria for treated epilepsy and were included in the study. Of these, 4,285 patients (66.3%) were still being followed up at the start of 2020. This equates to 46,120.9 patient years of data in total, with 7073.9 patient years of follow-up during the pandemic.

The demographic characteristics of these patients can be seen In Table 1 below.

N = 4285			
Sex	Male	2,212	51.6%
	Female	2,073	48.4%
Age	16-19	177	4.1%
	20-29	585	13.7%
	30-39	675	15.8%
	40-49	940	21.9%
	50-59	904	21.1%
	60-69	602	14.0%
	70+	402	9.4%

Table 1 – Summary of the demographic characteristics of the cohort at the start of 2020

Direct infection with COVID

During the pandemic period 160 patients (3.7%) had at least one inpatient hospital admission which was related to COVID-19, with 192 total admissions across all patients. The median length of stay was 8 days, and there were 37 cases where the patient was admitted to hospital for 30 days or more (19.3% of COVID-19 admissions).

Delivery of elective out-patient care

The proportion of patients with at least 1 outpatient clinic attendance at any outpatient clinic decreased during the pandemic period, especially during the second quarter of 2020, where only 25.5% of patients attended an outpatient clinic in comparison to 40.1% in the previous quarter and 41.9% in the second quarter of 2019.

The proportion of patients who attended neurology clinics remained relatively stable over the study period. The mean proportion of cohort patients reviewed within neurology outpatient clinics per quarter during the pandemic was 11.4%, compared to 12.1% during the two-year period preceding the pandemic and 10.4% over the whole pre-pandemic follow-up period (2012-2019). The proportion of patients attending neurology appointments during the pandemic was lowest in the third quarter of 2020, with 10.4% of patients attending compared to 11.0% in the same quarter of the previous year.

During the pandemic period, missed appointment rates dropped, with 83.5% of outpatient clinic appointments attended compared to 78.9% in the two years before the pandemic. These figures include both attendance at an in-person clinic or participation in a telephone appointment where relevant.

Unscheduled care- Hospital admissions and A&E attendance

The proportion of patients with epilepsy admitted to hospital for any reason reduced from a mean of 15.8% per quarter during 2019 to 12.5% in 2020, with a low of 9.7% during the

second quarter of 2020, which is down from 14.6% in the same quarter of 2019. (Figure 1). Epilepsy-related admissions decreased from an average of 4.9% of patients per quarter during 2019 to 3.5% during the second quarter of 2020 during the start of the first national lockdown and an average of 4.3% per quarter during the pandemic. The proportion of patients with epilepsy attending A&E attendance for any reason decreased during from a mean of 20.5% per quarter in 2019 to 16.8% in 2020, with a low of 14.6% during the second quarter of 2020, down 5.2% from the 19.8% attending in quarter 2 of 2019. The mean proportion of patients with an epilepsy-related A&E admission dropped from 2.5% per quarter during 2019 to 2.1% per quarter during 2020.

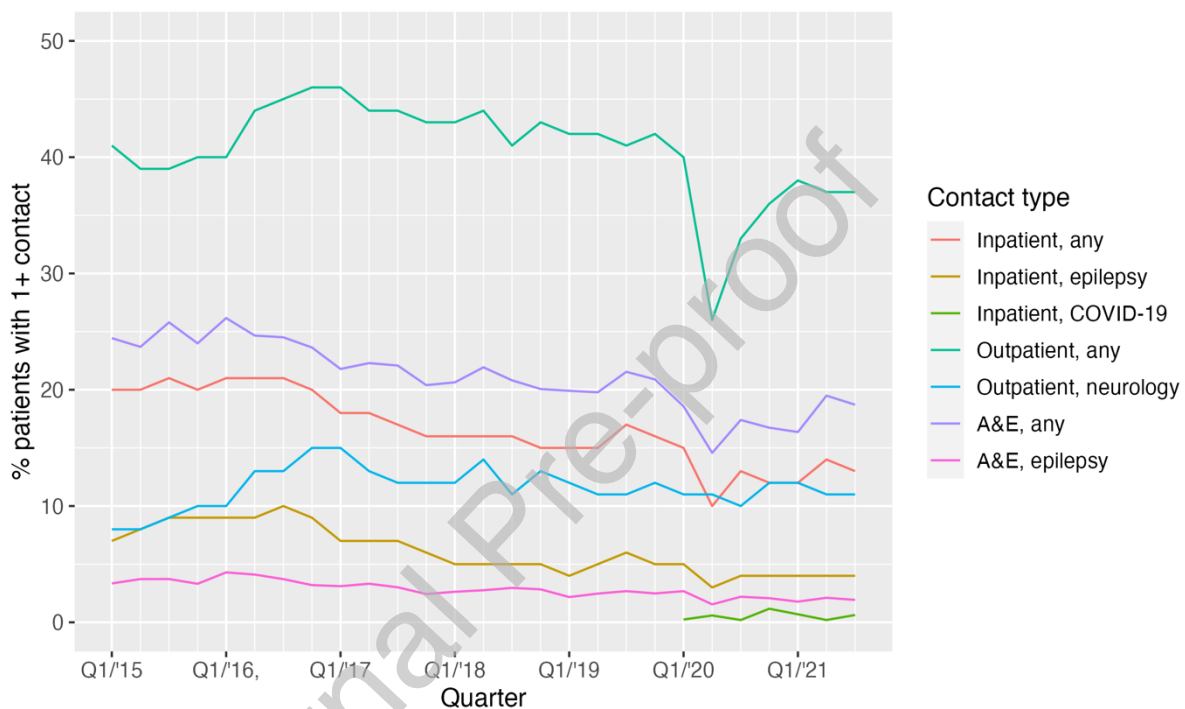


Figure 1 – Trends in the percentage of cohort patients with at least 1 admission or A&E attendance per quarter, 2015 to 2021

Deaths

In total, 453 (10.6%) cohort patients died between the start of 2020 and the end of follow-up - of these, 61 (12.4%) had COVID-19 listed as a contributing factor on their death record. Over a third of these deaths (22, 36.1%) occurred during the second quarter of 2020 at the start of the pandemic. Figure 2 shows the number of deaths per 100,000 patients in the NHS GGC health board area per quarter from 2012 to 2021. There was a statistically significant decrease in all-cause mortality of 0.25 deaths per 100,000 during pandemic compared to the pre-pandemic period ($p < 0.001$), and a decline in epilepsy-related deaths of 0.086 per 100,000 during pandemic years compared to the pre-pandemic period ($p = 0.02$).

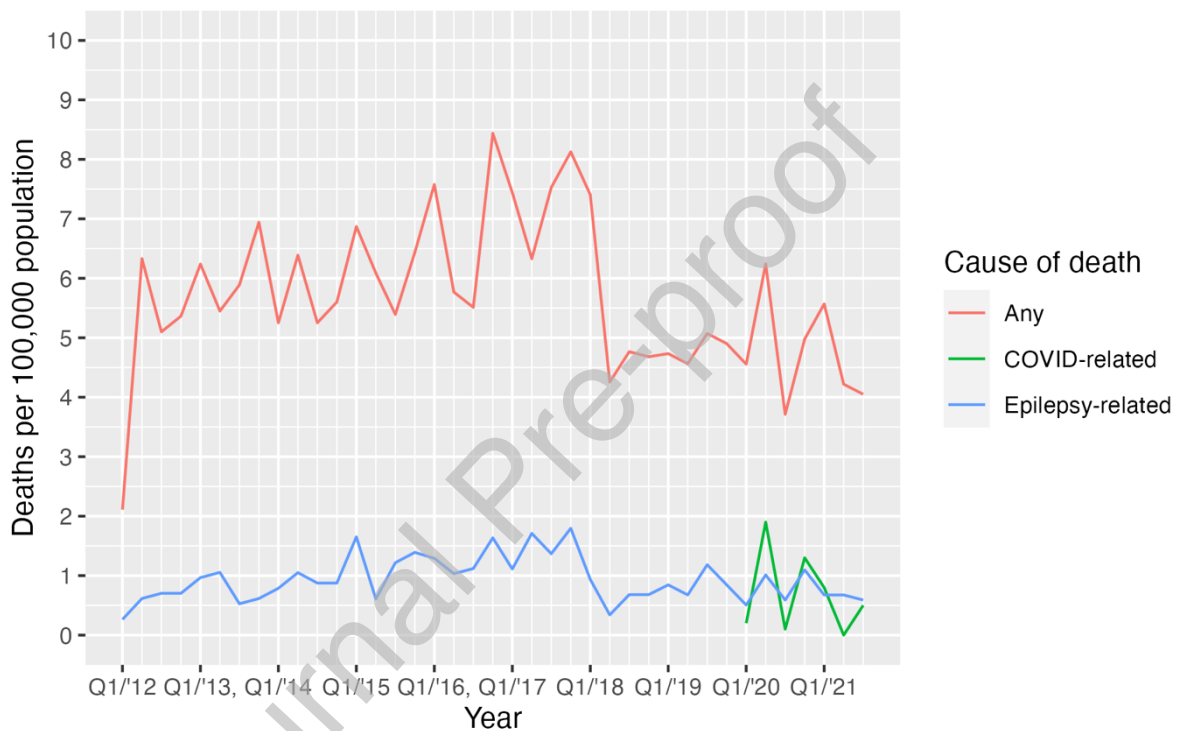


Figure 2 – Number of cohort deaths per 100,000 patients in NHS GGC health board area, 2012 - 2021

ASM prescribing

At the start of 2020 3,696 (86.3%) of the patients still being followed up were currently persistent with their ASM, with at least 1 ASM prescription dispensed in the 90 days. In total 1,044 patients (24.4%) discontinued their medications at least once during the pandemic, 244 (23.4%) of whom did not resume their medication. Of these patients, 654 (62.6%) discontinued their ASM after previously being persistent for more than 365 days, and 77 (11.7%) of these patients did not resume their medications before end of follow-up. Figure 3 shows the proportion of patients with at least 1 ASM prescription per quarter over the follow-up period – although there is a general downward trend over the course of the entire follow-up period which continues into the pandemic, more than 85% of cohort patients still had at least 1 prescription per quarter. As with the other results described above there were drops in the second quarter of 2020 and first quarter of 2021, corresponding to the strictest periods of national restrictions.

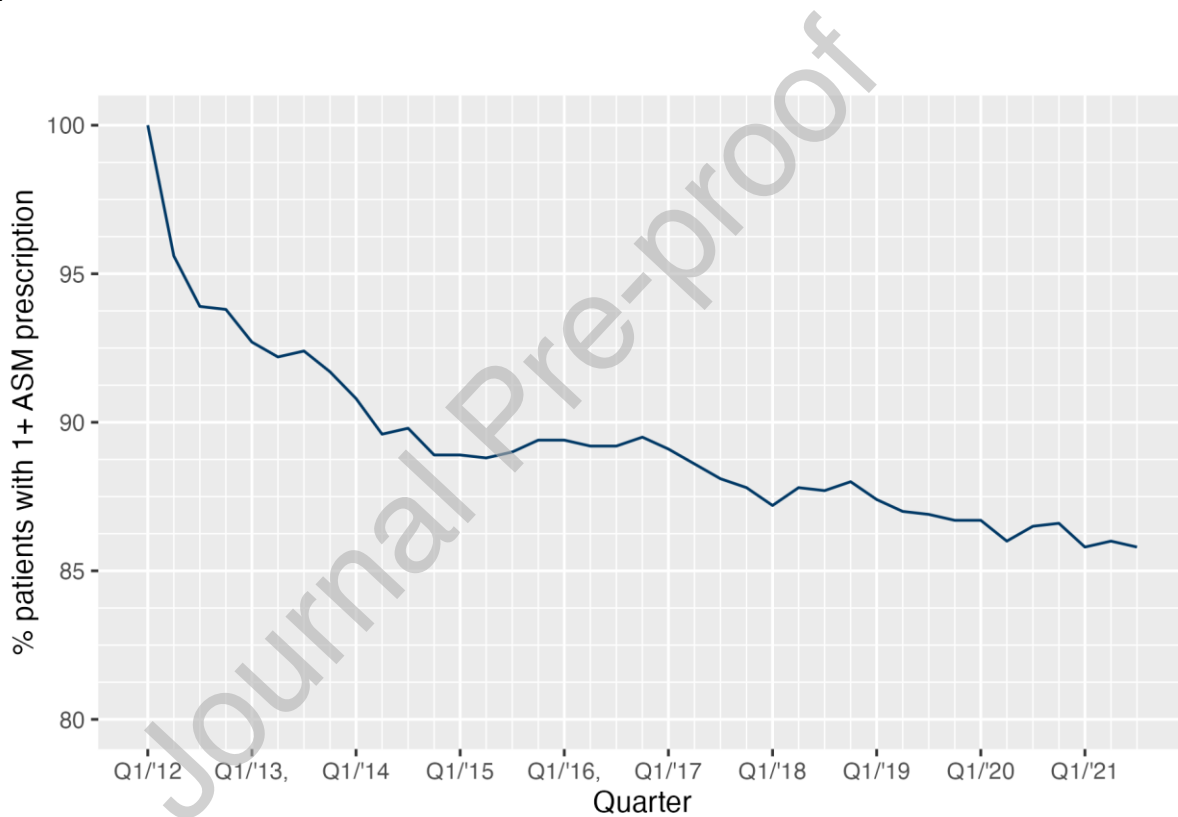


Figure 3 – Trend in the percentage of patients with at least 1 prescription for an ASM dispensed per quarter, 2012 - 2021

Mental health comorbidity

Between the start of the pandemic and the end of follow-up, 1,760 (41.1%) of total cohort patients received treatment for depression and 773 (18.0%) received treatment for anxiety, with a total of 1,999 patients having received treatment for at least one of the two conditions. Of these, 145 (8.2%) and 96 (12.4%) respectively had no records of received treatment for these conditions during the pre-pandemic follow-up period. Figure 4 shows the percentage of patients who had at least 1 relevant mental health prescription or admission per quarter during follow-up. The overall proportion of patients receiving at least 1 form of treatment for either depression or anxiety per quarter increased steadily over the follow-up period up until the pandemic period where it levelled out between 44% and 45%.

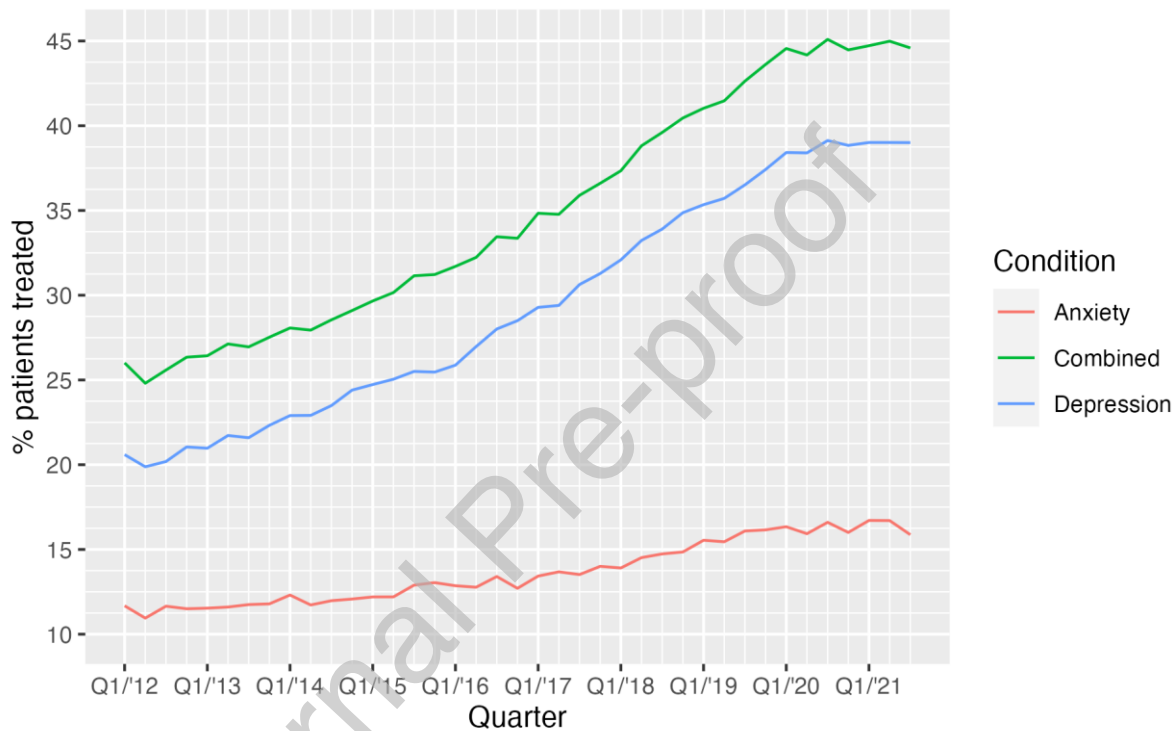


Figure 4 – Trends in the percentage of patients treated for mental health comorbidities per quarter 2012-2021

Discussion

Summary

The COVID-19 pandemic has had a significant impact on healthcare provision worldwide, the full extent of which we are only now beginning to understand. In this study we have used routinely collected data to assess the impact on a cohort of patients with epilepsy within the NHS Greater Glasgow and Clyde health board area in Scotland.

Despite concerns for the safety of vulnerable groups with chronic disease, we found that the overall rate of mortality decreased in people with epilepsy during the pandemic, with the biggest reduction being noted during the period of National Lockdown. A smaller but still significant downward trend was also noted in epilepsy related mortality, the strength of association in part explained by the smaller event rate. Although a definitive explanation to account for this remains unclear, it is not unreasonable to consider that the reduced mortality may reflect the adoption of a healthier lifestyle and less risk-taking behaviour during lockdown and potentially an improvement in medication adherence. If this hypothesis is correct, it gives hope to those working to improve outcomes in PWE and highlights that some of the excess mortality associated with epilepsy may be reversible.

The rapid adoption of telemedicine clinics (or alternatives) by those delivering care to people with epilepsy ensured continuity of care. It is reassuring that despite this novel method of out-patient care, objective measures of outcomes including rate of epilepsy related admissions and A&E admission reduced. The proportion of patients requiring in-patient care reduced in the second quarter of 2020 remained below pre-pandemic levels during follow up. Further qualitative, patient focused studies are required to ensure this method of delivery remains acceptable to PWE, as some health boards have elected to continue this as the default method of out-patient care.

Although the overall rate of mortality in this cohort decreased during the pandemic, COVID-19 remained an important cause of death accounting for 14.2% of total cohort deaths during the pandemic. Given the study design, we were unable to determine whether the rate of covid related death is greater than those in the general population with similar levels of comorbidity, although previous studies do not provide convincing evidence to support the hypothesis that PWE are at any specific increased risk of COVID-19.(3-6)

Depression and anxiety were both common in patients in this cohort throughout the study period with 41% and 18% of cohort patients respectively receiving treatment at some point. This is likely to reflect the very high levels of mental health comorbidity in PWE particularly in a hospital-based cohort where a larger proportion with have treatment resistant epilepsy.(20, 21) During the pandemic over 44% of cohort patients were treated for either depression or anxiety per quarter, a small proportion of whom had not previously been treated for either condition. Other studies based on survey data point to stress related to concerns around COVID-19 infection and the pandemic itself as a reason for increased stress and anxiety, but these results show that this did not result in a direct increase in the overall proportion of patients receiving medication for either in this cohort.(22) This could mean that the increased stress levels did not rise to the level of needing pharmacological treatment or that patients were not able to access primary care providers to get new

medications due to the pressure on the health service during this time, but more data would be required to draw a firm conclusion.

One strength of this study is the quality of the data used – within Scotland, most care for epilepsy is provided through the NHS, and CHI-linkage means that all available data on a patient's contact with NHS services can be identified to give a high level of data completeness as well as the potential for the long-term follow-up seen in this study.⁽²³⁾ To date, many of published studies that are smaller studies or case reports and thus the use of routinely collected data in this study helps to give another perspective and contribute further to our understanding of the issues faced by patients with epilepsy and the impact on the pandemic on the provision of healthcare. Additionally, the long period of pre-pandemic follow-up for this cohort enabled us to investigate the impact of the pandemic on long-term trends in various aspects of healthcare provision for these patients.

The study is not without its limitations. Analysis of additional data related to COVID-19 testing, infections that did not lead to hospitalisations, uptake of vaccinations, and data on patients access to primary care would allow for a more complete assessment of the impact of the pandemic on the patients in this cohort. Additionally, it is likely still too early to fully understand the long-term impact of COVID-19 infection on patients and the restrictions on service provision on those with long-term conditions who may have had treatments postponed. In addition, the persistence data shown is a poor surrogate marker for adherence and unlikely to pick up changes in subtle changes in adherence over a relatively short period with poor persistence requiring more than 90 days without ASM and dose instructions are required to provide more useful information.

Conclusion

This study shows that during a National Lockdown and the potential lifestyle changes that took place, mortality reduced in PWE. The provision of remote services allowed the maintenance of patient contact. Although further studies are required, this study gives some hope to those working with PWE that with an improvement in medication adherence, engagement with healthcare providers and an improved lifestyle some of the excessive mortality associated with epilepsy may be potentially reversible.

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Declarations of interest: none