Published in final edited form as:
Ann Epidemiol. 2014 November ; 24(11): 817–821.e2. doi:10.1016/j.annepidem.2014.08.004.

Elevated hepatic enzymes and incidence of venous thromboembolism: a prospective study

Aaron R. Folsom, MD[a,*], **Pamela L. Lutsey, PhD**[a], **Nicholas S. Roetker, BA**[a], **Wayne D. Rosamond, PhD**[b], **Mariana Lazo, MD, PhD**[c,d], **Susan R. Heckbert, MD, PhD**[e], **Saonli Basu, PhD**[f], **Mary Cushman, MD**[g,h], and **Elizabeth Selvin, PhD**[c,d]

[a]Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55454, USA.

[b]Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC 27514, USA.

[c]Division of General Internal Medicine, Department of Medicine, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA.

[d]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA.

[e]Department of Epidemiology, University of Washington, Seattle, WA 98101, USA.

[f]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN 55455, USA.

[g]Department of Medicine, University of Vermont, Burlington, VT 55446, USA.

[h]Department of Pathology, University of Vermont, Burlington, VT 05446 USA.

Abstract

Purpose—Approximately 10 percent of the general population have elevated blood concentrations of hepatic enzymes, which are linked to increased coagulation markers. We tested whether elevated hepatic enzymes are associated with increased risk of venous thromboembolism (VTE).

[*]Corresponding author: Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, Minnesota 55454 USA. Tel.: +1 (612) 626-8862. Fax: +1 (612) 624-0315. folso001@umn.edu. .
Folsom : folso001@umn.edu; Lutsey : Lutsey@umn.edu; Roetker : roetk001@umn.edu
wayne_rosamond@unc.edu
Lazo : mlazo@jhu.edu; Selvin : lselvin@jhsph.edu
Heckbert : heckbert@u.washington.edu
Basu : saonli@umn.edu; Cushman : Mary.Cushman@uvm.edu

Methods—We followed prospectively for VTE occurrence 12,604 adults with measurements of alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT).

Results—AST and GGT above the laboratory normal were associated over two decades of follow-up with increased risk of total (n = 532) and provoked VTE (n = 332), but with not unprovoked VTE (n = 200). In a model adjusted for age, race, sex, hormone replacement, alcohol intake, diabetes, body mass index, estimated glomerular filtration rate, and C-reactive protein, the hazard ratios (95% CI) for high versus normal AST were 1.46 (1.00, 2.11) for total VTE and 1.83 (1.21, 2.79) for provoked VTE. For high GGT, the hazard ratios were 1.34 (1.06, 1.69) for total VTE and 1.43 (1.07, 1.91) for provoked VTE. When follow-up was limited to the first 10-years, associations were even stronger (hazard ratios ≈ 1.7 for total VTE).

Conclusion—Elevated concentrations of two hepatic enzymes (AST and GGT) in this general middle-aged population are associated with a modestly increased risk of VTE.

Keywords

Venous thrombosis; Pulmonary embolus; Cohort study; Liver enzymes; Risk factors

Introduction

Chronic liver disease has long been considered to carry a high risk of hemorrhage. However, recent evidence suggests that decreased plasma coagulation factors are accompanied by decreased anticoagulant factors to offset bleeding [1]. Case reports indicate that besides portal vein thromboses, cirrhosis patients often develop leg deep vein thrombosis and therefore may have a thrombogenic diathesis [2,3]. A large case-control administrative database study in Denmark showed a 2-fold elevated venous thromboembolism (VTE) risk for both cirrhosis and non-cirrhotic liver disease [4]. Another administrative database study showed a modest increased risk of VTE in young (<45 y) cirrhosis patients compared with other young inpatients, but no increased risk for VTE in older cirrhosis patients [5]. In a nested case-control study in a general practice database, liver disease was associated with a 1.65 fold increase in VTE risk, but this result was not statistically significant [6]. In contrast with the several studies showing a positive association between liver disease and VTE, a population based case-control study showed an inverse association between liver disease and VTE [7].

More modest hepatic dysfunction than frank liver disease may also relate to VTE risk, but solid epidemiologic data are lacking. A recent body mass index (BMI)-matched clinical case-control study linked nonalcoholic fatty liver disease with a 2-fold elevated odds of VTE [8]. Nonalcoholic fatty liver disease is associated with elevated levels of hepatic enzymes [9] and increased levels or activity of several coagulation factor produced in the liver [10]. On the other hand, alcohol drinking, which can raise hepatic enzyme levels, generally has not been associated or was weakly inversely associated with VTE incidence [11]. Results from the National Health and Nutrition Examination Survey (NHANES 2005-2008) indicate that elevated hepatic enzymes are highly prevalent in the general population: i.e., elevated alanine transaminase (ALT), 10%; aspartate aminotransferase (AST), 16%; and gamma-

glutamyl transpeptidase (GGT), 9% [12]. Given findings to date and the high prevalence of hepatic dysfunction in the population, we prospectively assessed the association between hepatic enzyme levels and risk of VTE in the Atherosclerosis Risk in Communities (ARIC) Study.

Materials and Methods

Study Population

The ARIC Study [13] and its methods for identification and classification of VTE have been described in detail elsewhere [14,15]. In brief, 15,792 men and women aged 45 to 64 years enrolled in the ARIC study in 1987-1989, and had subsequent examinations in 1990-92, 1993-95, and 1996-98 and annual telephone contact. The present analysis used ARIC visit 2 as its start point for follow-up, because baseline samples are now scarce. The institutional review committees at each study center approved the methods and staff obtained informed participant consent.

Measurement of Hepatic Enzymes and VTE Risk Factors

Participants were asked to fast for 12 hours before their morning visit 2 appointments, and serum and plasma samples were obtained and stored at −80°C. Soon after the visit, central laboratories measured serum creatinine by the Jaffe method and glucose by a hexokinase assay. In 2012-13, a number of analytes, including hepatic enzymes, were measured on a previously unthawed visit 2 serum aliquot. Hepatic enzymes were measured on the Roche Modular P Chemistry analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Using duplicate samples collected at visit 2 and stored, we calculated the coefficients of variation (CVs), which were 16% for ALT, 6% for AST, and 4% for GGT. This CV encompasses variability related to both sample processing and laboratory methods. High sensitivity C-reactive protein (hsCRP) was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics) and read on the Roche Modular P Chemistry analyzer (CV 7%). Cystatin C was measured using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (CV 3%).

Diabetes was defined as a fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, a physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. Alcohol intake was derived from the usual number of drinks of beer, wine, or liquor reported to be consumed per week. Hormone replacement therapy (HRT) included estrogen replacement with or without progesterone, identified from pill bottles brought to the examination. Glomerular filtration rate (eGFR) was estimated from cystatin C and creatinine using the Chronic Kidney Disease Collaboration algorithm [16]. Body mass index was calculated as weight (kg)/height $(m)^2$. Factor VIII and activated partial thromboplastin time (aPTT) were available from the 1987-9 ARIC baseline visit [17,18].

VTE Occurrence

ARIC participants were contacted annually by phone and asked about all hospitalizations in the previous year. Hospital records with discharge diagnoses for possible VTE events, based

on a broad set of ICD-9CM discharge codes [14], were obtained from baseline through 2011. To validate the VTE events, two physicians (ARF, MC) reviewed the records using standardized criteria [14]. A diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) required positive imaging tests. We restricted DVTs for this analysis to those in the lower extremity or vena cava, because the vast majority of upper extremity DVTs were the result of in-dwelling catheters. Cases were classified by the reviewers as unprovoked (no obvious cause) or provoked (associated with recent hospitalization; cancer; major trauma; surgery; or marked immobility, such as being bed-ridden or having a fixed orthopedic cast).

Statistical Analysis

Of the 14,348 participants at ARIC visit 2, we successively excluded those who did not have any hepatic enzymes measured (n = 975), had a prior VTE (n = 260), were taking anticoagulants (n = 95), had heavy alcohol use (men >21 drinks/wk, women >14 drinks/wk) (n = 374), were not white or African American (n = 37), or had no follow-up after visit 2 (n = 3). (Those excluded for heavy alcohol use were 2-3 times as likely to have elevated hepatic enzyme concentrations.) This left 12,604 participants for the present analyses of incident VTE in relation to hepatic enzyme concentrations. Hepatic enzyme distributions were skewed and preliminary cubic spline graphs suggested non-linearity in relation to VTE. The enzymes therefore were analyzed as categories: (a) 5 categories with cutpoints at 25, 50, 75, and 90th percentiles of the whole distribution, (b) high/low based on the sex-specific upper limit cutpoints (in U/L) for normal ranges for the assays in our laboratory: ALT (women: 31, men: 41), AST (women: 31, men: 37), and GGT (women: 36, men: 61). Time at risk for VTE was computed from the date of visit 2 to the earliest of the following: date of hospital discharge with incident VTE, date of death, date of last follow-up contact, or end of follow-up.

Our main hypothesis was that hepatic enzyme levels would be associated positively with VTE incidence. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals of incident VTE. We verified the proportional hazards assumption of the Cox models by inspection of ln(-ln) survival curves for hepatic enzyme categories. We selected possible confounding variables for regression models based on our previous prospective findings on VTE risk factors [15,17,18]. Model 1 adjusted for age (continuous), sex, and race (African American, white); Model 2 for age, race, sex/HRT (men, women using HRT, women not using HRT), alcohol intake (continuous), diabetes status (yes or no), body mass index, eGFR and CRP (all continuous). Model 3 included two potential mediators, Factor VIII and aPTT (both continuous), from visit 1.

We also conducted three independent sensitivity analyses. Firstly, we removed from analysis VTE cases in the first three years of follow-up, in case these early cases were unusual. Secondly, we removed from analyses participants with obesity (BMI > 30 kg/m^2) at baseline, because we considered obese participants most likely to have non-alcoholic fatty liver disease. Thirdly, we truncated follow-up to 10 years, because hepatic enzyme levels at baseline would become less relevant during late follow-up.

Results

Descriptive Data

Among the 12,604 ARIC participants in this analysis, the median values (in U/L) for ALT, AST, and GGT were 14, 20, and 21, and the percentage with values above the upper limits of normal were 3%, 4%, and 13%, respectively. The Spearman correlation coefficient between ALT and AST was r = 0.63, between ALT and GGT was r = 0.45, and between AST and GGT was r = 0.33.

Table 1 shows participant characteristics according to sex-specific high versus normal hepatic enzyme categories. Using GGT as an example, participants with high GGT levels were more often African American, nonusers of HRT (in women), and diabetic, had higher mean values of BMI, CRP, and factor VIII, and shorter aPTT. Even though heavy alcohol users were excluded, average alcohol intake was higher in those with high GGT. On average those with high GGT drank 4.5 drinks per week, versus 3.3 drinks per week for those with normal GGT. With a few exceptions, findings were generally similar for ALT and AST.

VTE Incidence Across the Range of Hepatic Enzymes

Over a median of 20 years of follow-up, 532 incident lower extremity DVTs and/or PEs occurred, of which 200 were unprovoked. As shown in Table 2 for Model 2 and Supplemental Table 1 for all models, hepatic enzyme levels across the full range showed little association with VTE incidence. Compared with the first quartile (reference), hazard ratios for the middle quartiles and highest group of hepatic enzymes tended to be the same or slightly lower. For example, the Model 2 hazard ratios (95% CI) for VTE in relation to GGT categories were 1 (reference), 0.76 (0.58, 1.01), 0.91 (0.69, 1.21), 1.02 (0.75, 1.39), and 1.15 (0.82, 1.62). When VTE was stratified into unprovoked versus provoked, neither VTE type showed a significant adjusted association with ALT, AST, or GGT percentile groupings (data not shown).

VTE Incidence for High Versus Low Hepatic Enzymes

In contrast, when analyzed as abnormal (high) versus normal (Table 3 and Supplemental Table 2), high AST and GGT levels were associated with increased incidence of total and provoked VTE, though not unprovoked VTE. The Model 2 hazard ratios (95% CI) for high versus normal AST were 1.46 (1.00, 2.11) for total VTE and 1.83 (1.21, 2.79) for provoked VTE. For high GGT, the hazard ratios were 1.34 (1.06, 1.69) for total VTE and 1.43 (1.07, 1.91) for provoked VTE. These associations persisted after adjustment for aPTT and factor VIII (Model 3).

A supplemental analysis removing n = 27 VTEs occurring in the first three years of follow-up had little impact on the Model 2 hazard ratios in Table 3 (data not shown). In contrast, truncating follow-up to a maximum of 10 years (leaving n = 134 incident VTEs) strengthened the associations but widened the confidence intervals due to fewer events (Table 3). For example, the Model 2 hazard ratios (95% CI) for high versus normal AST through the first 10 years of follow-up were 1.74 (0.88, 3.44) for total VTE, 2.30 (1.05,

5.07) for provoked VTE, and 0.93 (0.22, 3.82) for unprovoked VTE. For high GGT, these respective hazard ratios were 1.70 (1.09, 2.65), 1.81 (1.03, 3.19), and 1.57 (0.77, 3.20).

In a sensitivity analysis restricting to participants without obesity (BMI < 30 kg/m^2) and leaving n = 307 VTEs (data not shown), the hazard ratios also were somewhat stronger than for Table 3. For example, the Model 2 hazard ratios (95% CI) for high versus normal AST in nonobese participants were 2.11 (1.33, 3.34) for total VTE and 2.55 (1.49, 4.36) for provoked VTE. For high GTT, these hazard ratios were 1.60 (1.16, 2.21) and 1.63 (1.09, 2.44), respectively.

Association of VTE Incidence with Alcohol Intake

Alcohol intake was weakly positively associated with total and provoked VTE incidence but not unprovoked VTE. In Model 2 but without hepatic enzymes in the model, the hazard ratios (95% CI) per 75 g/wk increment of alcohol intake were 1.15 (1.02, 1.29) for total VTE and 1.22 (1.06, 1.41) for provoked VTE. Adding any of the three hepatic enzymes to this model attenuated these alcohol hazard ratios only slightly (data not shown).

Discussion

In this prospective population based cohort, participants with values of GGT and AST above the normal range had 34 and 46 percent greater incidence of VTE over two decades of follow-up than did normal participants. The associations were stronger when follow-up was restricted to 10 years (70% and 74% increased 10-year risk for high AST and high GGT). The associations were independent of several VTE risk factors, and it was due to greater risk of provoked VTEs, rather than unprovoked. Within the normal range, higher values of hepatic enzymes did not increase VTE risk.

The precise reasons for individual participants having high GGT or AST are unknown. We excluded the heavy alcohol drinkers to remove this potential source of confounding, but self-reported alcohol intake is known to be somewhat misclassified. Even with the exclusion, hepatic enzyme levels remained positively associated with alcohol intake, and associated with most other measured VTE risk factors (Table 1 and Supplemental Table 1). However, we adjusted for all of these factors, including alcohol, which itself was weakly positively associated with VTE risk, in contrast with most previous epidemiologic studies of alcohol and VTE [11].

ARIC did not have information to exclude medical conditions that might have caused elevations in visit 2 hepatic enzyme levels, such as cirrhosis or metastatic cancer. However, most of these are rare in a general population cohort. A significant proportion of elevated values not due to alcohol might be expected to be from nonalcoholic fatty liver disease [9,19]. Previous studies of VTE and diagnoses of severe liver disease [4-7] or nonalcoholic fatty liver disease [8] have generally shown positive associations with VTE risk, but not uniformly. Arguing against nonalcoholic fatty liver disease being the link between elevated hepatic enzymes and VTE in this cohort is the fact that the association was stronger after removing participants with obesity, who are most likely to have nonalcoholic fatty liver

disease. Additionally, the associations observed between ALT, the most liver specific enzyme, and VTE were all null.

Elevated hepatic enzyme values are certainly not a “cause” of VTE, but mild hepatic dysfunction may increase production of cytokines and coagulation factors, leading to a thrombotic diathesis. Nonalcoholic fatty liver disease is associated with increased levels or activity of several coagulation factors [10]. In our study, higher GGT was associated with higher factor VIII and shorter aPTT, which are both VTE risk markers [17,18]. Adjustment for factor VIII and aPTT did not explain the association of high AST and GGT with increased VTE risk, but this may not be surprising, as the hemostasis markers were measured three years before the blood for hepatic function tests.

High AST and GGT were associated with provoked VTEs only, which included 62 percent of all VTEs. The designation of “provoked” was assigned by the study physicians adjudicating the VTE events, who were masked to the hepatic enzyme values. It was defined as VTE due to recent hospitalization, cancer, major trauma, surgery, or marked immobility [14], but not conditions like obesity, hormone replacement therapy, or short plane or car rides. VTEs without obvious precipitants defined as “unprovoked,” but of course a triggering factor may not have been documented in the medical record. Because the provoking conditions were at the time of VTE, up to 18 years after hepatic function assessment, it is unlikely that the provoking factors, unless longstanding, caused the elevated AST or GGT. A previous analysis in an earlier set of VTEs showed that most baseline characteristics examined were similar between provoked and unprovoked VTE, except for a somewhat greater history of cancer at baseline in those who later had a provoked VTE (13% versus 10% for unprovoked) [14]. Those with elevated baseline AST or GGT may have been more likely over the ensuing years to have developed medical conditions leading to VTE. Thus, the argument that hepatic dysfunction leads to VTE in a causal fashion is weakened by the absence of an association with unprovoked VTE. However, statistical power was less for unprovoked VTE, which was rarer than provoked VTE. Nevertheless, irrespective of the causal pathways, elevated AST or GGT does mark a small group of middle-aged adults at increased VTE risk.

Some other methodologic aspects of this study warrant consideration. Firstly, being a cohort study, we documented that elevated AST and GGT preceded VTE onset. However, we had only a single measurement and over the long follow-up period participants may have changed between high versus normal categories. Such misclassification typically would weaken the observed association between AST and GGT, so the real association may be stronger as evidenced by the sensitivity analysis restricted to 10 years of follow-up. Secondly, samples were stored unthawed at −80°C for two decades prior to measurement of hepatic enzyme levels. At −80°C, AST is stable at least two years [20]. We also found hepatic enzymes associated as expected with alcohol intake, sex, and other factors. Any deterioration in the freezer would most likely bias hazard ratios toward the null. Thirdly, the prevalence of elevated hepatic function tests was lower in ARIC than reported by NHANES [12]. This might be explained by differences in study date (ARIC 1990-92 vs. NHANES 2005-8); differences in the prevalence of obesity; ARIC’s exclusion of individuals with heavy alcohol consumption; or different laboratory reference values for elevated hepatic

enzymes. In the absence of a standard definition of “elevated” hepatic enzymes, ARIC used the cut-off provided by the manufacturer of the assay. It has been documented the range of upper limits of normal for hepatic enzymes can vary widely [21]. Nevertheless, it seems unlikely that these differences between ARIC and NHANES would affect the internal validity of ARIC’s findings. Finally, only hospitalized VTE events were captured; yet, several pilot studies in ARIC have suggested that the vast majority of initial VTEs are hospitalized.

In conclusion, elevated levels of AST and GGT in this general middle-aged population are associated with a modestly increased risk of VTE over the next two decades.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All authors contributed to the preparation of this manuscript. The authors thank the staff and participants of the ARIC study for their important contributions.

Sources of Funding: This study was funded by National Institute of Diabetes and Digestive and Kidney Diseases grant R01 DK089174, National Heart, Lung, and Blood Institute grant R01 HL059367, and Atherosclerosis Risk in Communities (ARIC) Study contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C. Roche Diagnostics provided material support (reagents) for the hepatic enzyme assays.

List of abbreviations

ARIC	Atherosclerosis Risk in Communities
VTE	venous thromboembolism
ALT	alanine transaminase
AST	aspartate aminotransferase
GGT	gamma-glutamyl transpeptidase
CI	confidence interval
NHANES	National Health and Nutrition Examination Survey
CVs	coefficients of variation
hsCRP	high sensitivity C-reactive protein
eGFR	glomerular filtration rate
aPTT	activated partial thromboplastin time
ARF	Aaron R. Folsom
MC	Mary Cushman
DVT	deep vein thrombosis
PE	pulmonary embolism

HR	hazard ratio
HRT	hormone replacement therapy
BMI	body mass index

References

[1]. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011; 365(2): 147–56. [PubMed: 21751907]

[2]. Lippi G, Targher G, Favaloro EJ, Franchini M. Venous thromboembolism in chronic liver disease. Semin Thromb Hemost. 2011; 37(1):66–76. [PubMed: 21305802]

[3]. Ali M, Ananthakrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: a nationwide analysis. Dig Dis Sci. 2011; 56(7): 2152–9. [PubMed: 21279685]

[4]. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol. 2009; 104(1):96–101. [PubMed: 19098856]

[5]. Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. Clin Gastroenterol Hepatol. 2010; 8(9):800–5. [PubMed: 20566312]

[6]. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med. 2007; 167(9):935–43. [PubMed: 17502535]

[7]. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000; 160(6):809–15. [PubMed: 10737280]

[8]. Di Minno MN, Tufano A, Rusolillo A, Di Minno G, Tarantino G. High prevalence of nonalcoholic fatty liver in patients with idiopathic venous thromboembolism. World J Gastroenterol. 2010; 16(48):6119–22. [PubMed: 21182227]

[9]. Daniel S, Ben-Menachem T, Vasudevan G, Ma CK, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol. 1999; 94(10):3010–4. [PubMed: 10520861]

[10]. Kotronen A, Joutsi-Korhonen L, Sevastianova K, Bergholm R, Hakkarainen A, Pietiläinen KH, et al. Increased coagulation factor VIII, IX, XI and XII activities in non-alcoholic fatty liver disease. Liver Int. 2011; 31(2):176–83. [PubMed: 21134109]

[11]. Lutsey PL. Invited commentary: Diet and risk of venous thromboembolism – a hard nut to crack. Am J Epidemiol. 2012; 175(2):127–30. discussion 131-2. [PubMed: 22180876]

[12]. Tsai J, Ford ES, Li C, Zhao G. Past and current alcohol consumption patterns and elevations in serum hepatic enzymes among US adults. Addict Behav. 2012; 37(1):78–84. [PubMed: 21975024]

[13]. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989; 129(4):687–702. [PubMed: 2646917]

[14]. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the Longitudinal Investigation of Thromboembolism Etiology. Am J Med. 2004; 117(1):19–25. [PubMed: 15210384]

[15]. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the Longitudinal Investigation of Thromboembolism Etiology. Arch Intern Med. 2002; 162(10):1182–9. [PubMed: 12020191]

[16]. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. for the CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367(1):20–9. [PubMed: 22762315]

[17]. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracey RP, Aleksic N, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). Am J Med. 2002; 113(8):636–42. [PubMed: 12505113]

[18]. Zakai NA, Ohira T, White R, Folsom AR, Cushman M. Activated partial thromboplastin time and risk of future venous thromboembolism. Am J Med. 2008; 121(3):231–8. [PubMed: 18328308]

[19]. Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol. 2013; 178(1):38–45. [PubMed: 23703888]

[20]. Paltiel L, Rønningen KS, Meltzer HM, Baker SV, Hoppin JA. Evaluation of freeze thaw cycles on stored plasma in the Biobank of the Norwegian Mother and Child Cohort Study. Cell Preserv Technol. 2008; 6(3):223–30. [PubMed: 20428472]

[21]. Neuschwander-Tetri BA, Unalp A, Creer MH, for the Nonalcoholic Steotohepatitis Clinical Research Network. Influence of local reference populations on upper limits of normal for serum alanine aminotransferase levels. Arch Intern Med. 2008; 168(6):663–6. [PubMed: 18362260]

Highlights

- Concentrations of hepatic enzymes are often elevated in the general population.
- Whether this increases risk venous thromboembolism (VTE) risk is unknown.
- We found elevated concentrations of two hepatic enzymes (AST and GGT) associated with a 40% increased VTE incidence.
- Patients with elevated hepatic enzymes warrant consideration for thrombosis risk.

Table 1

Characteristics of participants [mean (SD) or %] in relation to normal or high categories of hepatic function tests, ARIC, 1990-1992

	ALT		AST		GGT	
	Normal	**High***	**Normal**	**High***	**Normal**	**High***
Number of participants**	12,208	396	12,107	497	10,937	1,666
Age, years	56.9 (5.7)	55.4 (5.3)	56.9 (5.7)	56.6 (5.5)	56.9 (5.7)	56.8 (5.6)
African Americans, %	25.3	22.0	25.0	30.0	23.1	38.7
Hormone replacement use in women, %	25.8	19.2	25.9	17.4	27.2	16.9
Body mass index, kg/m^2	27.9 (5.4)	30.4 (5.6)	27.9 (5.4)	29.5 (5.8)	27.7 (5.2)	30.0 (6.1)
Diabetes, %	14.4	28.8	14.4	25.2	12.4	30.6
Alcohol intake (g/wk)	25.4 (52.7)	27.3 (57.8)	25.2 (52.5)	32.3 (60.6)	24.6 (51.5)	30.6 (60.9)
eGFR, mL/min/1.73m^2	95.3 (17.0)	94.2 (16.9)	95.4 (16.9)	91.7 (18.9)	95.3 (16.6)	94.5 (19.6)
C-reactive protein, mg/L	4.3 (7.2)	5.7 (8.2)	4.3 (7.1)	6.1 (9.3)	4.0 (6.7)	6.8 (9.7)
Factor VIII, %†	130 (38)	137 (41)	130 (38)	141 (47)	128 (36)	142 (46)
aPTT, seconds†	29.1 (3.0)	28.7 (3.1)	29.1 (3.0)	29.1 (3.7)	29.2 (3.0)	28.7 (3.1)

*Cutpoints for high in women/men: ALT – 31/41 U/L, AST – 31/37 U/L, GGT – 36/61 U/L.

**N's vary between 12,414 and 12,604 because of characteristics missing on some participants.

†Value from 1987-89.

Table 2

Model 2 hazard ratio (95% confidence interval) of venous thromboembolism (VTE) incidence in relation to percentiles of hepatic function tests, ARIC, 1990-2011

		Percentile				
		0-24	**25-49**	**50-74**	**74-89**	**≥90**
Alanine Transaminase (U/L)		≤10	11-13	14-18	19-25	≥26
Incidence rate (95% CI)		2.3 (1.9, 2.8)	2.2 (1.8, 2.6)	2.5 (2.1, 2.9)	2.5 (2.0, 3.0)	2.5 (1.9, 3.2)
	N events	113	102	156	96	58
	Person-years	49264	47595	61696	38224	23527
Model 2	HR (95% CI)	1 (Ref.)	0.88 (0.67, 1.15)	1.00 (0.78, 1.27)	0.94 (0.71, 1.24)	0.91 (0.66, 1.27)
Aspartate Aminotransferase (U/L)		≤16	17-19	20-22	23-27	≥28
Incidence rate (95% CI)		2.2 (1.9, 2.7)	2.3 (2.0, 2.8)	2.4 (2.0, 2.8)	2.7 (2.2, 3.3)	2.3 (1.8, 3.0)
	N events	115	134	116	104	56
	Person-years	51312	58288	48821	38451	23434
Model 2	HR (95% CI)	1 (Ref.)	1.00 (0.78, 1.29)	0.99 (0.76, 1.29)	1.12 (0.85, 1.47)	0.92 (0.66, 1.27)
Gamma-Glutamyl Transpeptisase (U/L)		≤13	14-20	21-32	33-52	≥53
Incidence rate (95% CI)		1.9 (1.6, 2.4)	1.9 (1.6, 2.3)	2.6 (2.2, 3.0)	3.1 (2.5, 3.7)	3.2 (2.6, 4.1)
	N events	93	114	150	99	69
	Person-years	48931	60558	57825	32124	20848
Model 2	HR (95% CI)	1 (Ref.)	0.76 (0.58, 1.01)	0.91 (0.69, 1.21)	1.02 (0.75, 1.39)	1.15 (0.82, 1.62)

Model 2: Adjusted for age, race, sex/HRT, alcohol intake, diabetes, BMI, eGFR, CRP.

Table 3

Model 2 hazard ratio (95% confidence interval) of venous thromboembolism (VTE) incidence in relation to high versus normal hepatic function tests, ARIC, 1990-2011

			ALT		AST		GGT	
			Normal	High*	Normal	High*	Normal	High*
Total	VTE Incidence rate (95% CI)		2.4 (2.2, 2.6)	2.2 (1.3, 3.6)	2.3 (2.1, 2.6)	3.7 (2.6, 5.2)	2.3 (2.1, 2.5)	3.4 (2.7, 4.1)
		N events	510	15	495	30	433	92
		Person-years	213571	6735	212331	7976	193352	26934
	Model 2	HR (95% CI)	1 (Ref.)	0.90 (0.54, 1.51)	1 (Ref.)	1.46 (1.00, 2.11)	1 (Ref.)	1.34 (1.06, 1.69)
		HR for first 10 years (95% CI)	1 (Ref.)	1.50 (0.66, 3.43)	1 (Ref.)	1.74 (0.88, 3.44)	1 (Ref.)	1.70 (1.09, 2.65)
Unprovoked VTE		N events	192	3	189	6	166	29
		Person-years	209331	6575	208243	7663	189766	26121
	Model 2	HR (95% CI)	1 (Ref.)	0.49 (0.16, 1.55)	1 (Ref.)	0.81 (0.36, 1.83)	1 (Ref.)	1.17 (0.78, 1.77)
		HR for first 10 years (95% CI)	1 (Ref.)	0.63 (0.09, 4.56)	1 (Ref.)	0.93 (0.22, 3.82)	1 (Ref.)	1.57 (0.77, 3.20)
Provoked VTE		N events	318	12	306	24	267	63
		Person-years	211110	6696	209903	7903	191192	26594
	Model 2	HR (95% CI)	1 (Ref.)	1.12 (0.63, 2.01)	1 (Ref.)	1.83 (1.21, 2.79)	1 (Ref.)	1.43 (1.07, 1.91)
		HR for first 10 years (95% CI)	1 (Ref.)	2.02 (0.80, 5.06)	1 (Ref.)	2.30 (1.05, 5.07)	1 (Ref.)	1.81 (1.03, 3.19)

*Cutpoints for high in women/men: ALT – 31/41 U/L, AST – 31/37 U/L, GGT – 36/61 U/L.

Model 2: Adjusted for age, race, sex/HRT, alcohol intake, diabetes, BMI, eGFR, CRP.