HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2015 June 16.

Published in final edited form as:

J Am Geriatr Soc. 2013 January ; 61(1): 132–136. doi:10.1111/jgs.12044.

Transferrin Saturation and Hospital Length of Stay and Mortality in Medicare Beneficiaries

Arch G. Mainous III, PhD[*], **Vanessa A. Diaz, MD, MS**[*], **Michele E. Knoll, MA**[*], **Mary M. Hulihan, MPH**[†], **Althea M. Grant, PhD**[†], and **Robert U. Wright, MPH**[*]

[*]Department of Family Medicine, Medical University of South Carolina, Charleston, South Carolina

[†]Division of Blood Disorders, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

OBJECTIVES—To evaluate in a large, nationally representative cohort the association between high serum transferrin saturation (TS) and hospital length of stay and mortality in older adults.

DESIGN—Prospective cohort.

SETTING—Longitudinal analyses of the Third National Health and Nutrition Examination Survey linked to Medicare claims from 1991 through 2006.

PARTICIPANTS—Medicare beneficiaries aged 65 and older at baseline.

MEASUREMENTS—Transferrin saturation collected on each participant at baseline was characterized as <20.0%, 20.0% to 54.9%, and 55.0% and greater. Length of stay in the hospital and death in the hospital were primary outcomes. Analyses were adjusted for age, sex, race and ethnicity, education, and severity of illness.

RESULTS—Individuals hospitalized during the study period (79.4%) with high (odds ratio (OR) = 2.54, 95% confidence interval (CI) = 1.05–6.12) or low (OR = 1.31, 95% CI = 1.07–1.62) TS had a significantly greater risk of death than those with moderate TS. Individuals with high TS had longer average length of stay per hospitalization (11.1 days, (standard error, SE 1.7 days), $P = .01$) than those with moderate TS (8.4 (0.3) days). Individuals with high TS also had more hospital days per year (8.6 (2.0) days, $P = .04$) than those with moderate TS (6.7 (0.5) days).

CONCLUSION—High TS is associated with longer length of stay and death in the hospital (unweighted N = 3,847, weighted N = 28,395,464).

Keywords

transferrin saturation; National Health and Nutrition Examination Survey; Medicare; mortality

Address correspondence to Arch G. Mainous III, Department of Family Medicine, Medical University of South Carolina, 295 Calhoun St., Charleston, SC 29425. mainouag@musc.edu.

Author Contributions: All authors contributed significantly to this work. All authors drafted and reviewed the subsequent versions of the manuscript and approved the final version.

Conflict of Interest: There are no potential conflicts of interest for any author. The authors declare no competing financial interests.

Serum transferrin saturation (TS) is a commonly used first-step measure in detecting hereditary iron overload in clinical practice and is recommended strategy in several guidelines.[1–5] Evidence from large longitudinal cohort studies in the general population shows that high TS saturation is associated with greater risk of morbidity, from cancer for example, and all-cause mortality.[6–8] A recent meta-analysis of general population studies supported the greater mortality risk associated with high levels of TS.[9]

In contrast, several studies have not found a link between high TS levels and mortality.[10,11] Initial steps in screening for hemochromatosis or iron overload is based on high TS is recommended based on TS greater than 45%, a level found in approximately 6% of the adult U.S. population.[12,13] It is likely in the studies that did not find an effect that their results were due to categorization of their high group according to sample quartiles or quintiles, placing many individuals with normal TS into those studies' high group (e.g., TS >29% in postmenopausal women would be considered high) and decreasing the likelihood of observing an effect of high TS.[10,11] Many people are not evaluated for high TS and are therefore not diagnosed, even though detection and treatment are easy and inexpensive.[12–14]

It is unclear whether these deleterious effects of high TS seen with the development of disease or mortality affect hospital length of stay, particularly in older adults. Length of stay and mortality in the hospital are important outcomes for older adults.[15] These factors are important for a variety of reasons, including healthcare use, and economic burden.[15] Consequently, the purpose of this study was to evaluate, in a large, nationally representative cohort, the association between high serum TS and hospital length of stay and mortality in Medicare beneficiaries aged 65 and older.

METHODS

Longitudinal analyses were conducted using data from the third National Health and Nutrition Examination Survey (NHANES III) linked to Medicare claims from 1991 through 2006.[16] NHANES III provides population estimates of the United States and was conducted from October 1988 through October 1994. It used complex, multistage, stratified, clustered samples of civilian, noninstitutionalized populations. Thirty thousand eight hundred eighteen persons were examined in mobile examination centers (MECs) that visited 89 communities across the United States. The cohort for the current study consisted of all persons aged 65 and older at the time of their MEC visit. The health examination included collection of blood and urine specimens for various laboratory analyses.

Risk of hospitalization, death in the hospital, and hospital length of stay variables were investigated using the NHANES III data linked with Centers for Medicare and Medicaid Services (CMS) Medicare enrollment and claims files. Because of confidentiality concerns associated with this data, the National Center for Health Statistics (NCHS) Research Data Center linked the data and supplied it for analysis. Records from January 1, 1991, through December 31, 2006, were used. Death certificate data found in the National Death Index (NDI) that had been linked to the NHANES III data were also used. The NCHS Research Data Center merged the NDI data with the other files. The National Center for Health

Statistics has had good success merging data sets like the NDI with the NHANES, with evidence of a greater than 98% match.[17]

Although CMS data were available through December 31, 2007, NDI data were available only through December 31, 2006, so December 31, 2006, was used as the end of the study period. The time period of interest was from January 1, 1991, or the date of the MEC visit if it was later, through the date the subject joined a health maintenance organization (HMO) after which they had no more claims in the CMS data, died, or the end of the study period (December 31, 2006).

The Medical University of South Carolina institutional review board approved this project.

Transferrin Saturation

Serum iron and total iron-binding capacity (TIBC) were measured in serum, and was TS calculated by dividing serum iron by TIBC and multiplying by 100. TS was categorized as less than 20.0%, 20.0% to 54.9%, and 55.0% or greater. Although there is not universal agreement on the upper and lower limits of normal TS, these cut points correspond to several conventional standards.[18] Moreover, previous studies of TS and mortality risk found an association between mortality and TS at TS levels of 55% or higher.[6] The middle category was used as the reference in each analysis.

Covariates

Covariates used in the analyses were age at baseline in NHANES III, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), education (<12th grade, high school, and >high school), and severity of illness as measured according to the Charlson Comorbidity Index,[19] a commonly used measure of severity of illness, includes 1 point each for heart attack, congestive heart failure, stroke, chronic bronchitis or emphysema, lupus, diagnosed or undiagnosed diabetes mellitus (glycohemoglobin > 6.5%),[20] ulcer, and liver disease (high alanine aminotransferase (ALT) or aspartate aminotransferase (AST)). AST greater than 37 U/L or ALT greater than 40 U/L in men, or AST greater than 31 U/L or ALT greater than 31 U/L in women indicated liver disease.[21] Also included with 2 points each were cancer (other than skin cancer), diabetic retinopathy, paralysis in hands or legs, leukemia, lymphoma, and renal disease (urinary albumin to urinary creatinine ratio > 30).[22]

Outcomes

Variables evaluated were hospitalization, death in the hospital, average length of stay per hospitalization, average number of hospital days per year, and average number of hospital stays per year. Although the NDI is not limited to documenting death in the hospital, this study was limited to death in the hospital.

Analysis

The relationship between sex and other demographic variables was first evaluated using chi-square analysis. Whether a subject had ever stayed in the hospital and time to the first hospitalization were analyzed based on Medicare Provider Analysis and Review (MEDPAR) records.[23] Risk of hospitalization was tested using a survival analysis adjusted

for age, sex, race and ethnicity, education, and Charlson Comorbidity Index. Survival analysis was used for this test because persons who joined an HMO might have had a different length of time available for follow-up than those who had claims data throughout the study period.

In individuals who were hospitalized, death in the hospital was then investigated also based on MEDPAR records. Risk of death in the hospital was evaluated in a logistic regression adjusted for the same covariates as the survival analysis for risk of hospitalization. Logistic regression was chosen rather than a proportional hazards model for risk of death within the hospital because the analysis was limited to people who had been hospitalized. The length of stay variables (length of stay in a hospital, hospital days per year, and number of hospital stays) were further evaluated in individuals who did not die in the hospital using predicted marginals in linear regressions adjusted for the aforementioned set of covariates. Predicted marginals are a generalization of adjusted means and were used to represent adjusted means.[24] Average length of stay was derived from these numbers. Those unlogged values are presented for context. This variable was transformed using the natural log of length of stay because of the nonnormal distribution of length of stay, and this was used for the actual significance test. The average number of hospitalized days per year was also computed based on the total number of days in the hospital divided by the total number of years of follow-up in the study period. This measure was also log transformed.

The average number of hospital stays per year was computed. Number of stays was not log transformed for analysis because its distribution more closely resembled a normal distribution. These analyses were adjusted for the aforementioned set of covariates.

All analyses were performed using SUDAAN (SUDAAN Statistical Software Center, Research Triangle Park, NC), and the appropriate weighting and design variables were used to generate population estimates for the United States.

RESULTS

Demographic characteristics of the cohorts are shown in Table 1. A total of 1.2% of the cohort had TS greater than 55%. The unweighted N was 3,847, with a population estimate of 28,395,000. The proportion of participants hospitalized during the study period was 79.4%. The primary diagnoses for hospitalization episodes for each of three TS groups are presented in Table 2. Based on the three-digit stem for International Classification of Diseases, Ninth Revision, codes, there was a high degree of similarity between the groups, with heart failure, pneumonia, and other cardiac disease being present in all groups.

The survival analysis for risk of future hospitalization indicated no difference between persons with TS of 55.0% or greater (hazard ratio (HR) = 0.86, 95% confidence interval (CI) 0.60–1.23) or TS less than 20.0% (HR = 1.04, 95% CI 0.92–1.17) and those in the reference category of moderate levels of TS (20.0–54.9%).

When the analysis was reduced to individuals who were hospitalized, the logistic regression for death in the hospital showed that individuals with high or low TS had a significantly greater risk of death than the reference category of those with moderate TS (Table 3). In

terms of the proportion of individuals dying in the hospital in each group, 51.7% of those with TS of 55.0% or greater, 27.9% of those with TS from 20.0% to 54.9%, and 34.7% of those with TS less than 20.0% died in the hospital. The analysis had a mean of 7.4 years of follow-up to death. Table 4 indicates that the average length of stay per hospitalization and average hospital days per year were significantly higher in subjects with TS of 55.0% or greater than in those in the moderate TS group.

DISCUSSION

The results of this investigation indicate that high TS is associated with greater risk of death in the hospital, longer length of stay per episode, and more hospital days per year. This effect was present after controlling for age, sex, race, severity of illness, and access to care. These results are consistent with previous findings describing other risks associated with high TS, such as all-cause mortality and disease development when TS is 55.0% or greater. Together, these findings suggest that high TS is a marker of underlying physiological changes that increase the risk of morbidity and mortality.[6–9] High TS was not associated with more hospital stays per year. Further studies are needed to evaluate whether interventions to decrease TS could have a physiological effect and thus improve these health outcomes.

Although only 1.2% of these Medicare beneficiaries had high TS, they accounted for more than 341,000 individuals who are at greater risk for longer lengths of stay in the hospital, more hospitalized days per year, and death in the hospital. This group of Medicare beneficiaries receives public financing of their health care, so the additional costs due to more hospitalized days is passed on to the federal government and the taxpayer. Because high TS is easily detectable and treated, this question of Medicare spending due to a potentially preventable cause is particularly germane in a time when the federal budget deficit is high. These results also indicate that the types of diagnoses for which individuals with high TS are hospitalized are similar to those of other individuals with normal TS, suggesting that diagnosis upon hospitalization may not suggest further need for investigation into high TS by healthcare providers. More-aggressive screening and detection of high TS may be warranted.

A possible mechanism for why high TS could result in poor outcomes even after accounting for factors such as severity of illness could be because high TS is associated with oxidative stress.[25] High TS is also associated with cellular toxicity.[25] This general mechanism has implications for worse outcomes across a variety of diseases and organ systems.[26,27]

In addition to the finding that high TS is associated with greater risk of death in the hospital and longer length of stay, low TS was also associated with greater risk of death and more days in the hospital. It is unclear why low TS would be associated with these outcomes, but it is possible that these low levels of TS represent iron deficiency, a condition associated with morbidity.[28] Iron-deficiency anemia is associated with low TS, low serum ferritin, and low hemoglobin and is a common hematological abnormality in older individuals that is associated with morbidity.[29,30] Adequate iron stores are also necessary for several nonerythropoietic biologic processes such as preservation of immune function,

thermoregulation, and cognition. Impairment of these processes due to low TS could lead to greater mortality.

There are several strengths of this study. First, it used a nationally representative cohort in whom the independent variable of TS and measures needed to compute severity of illness (e.g., glycohemoglobin for undiagnosed diabetes mellitus, liver function tests, albumin creatinine ratio) were collected according to a standardized protocol. This methodology is less likely to result in measurement bias than studies using only self-reports or data that may have been inconsistently collected in electronic health records. Second, the study used a population of Medicare beneficiaries. This is particularly important because lack of insurance has been shown to have a significant effect on hospital length of stay.[31,32]

One limitation of this study was the small percentage of persons with high TS (≥ 55.0%), which allowed reliable estimates for the most general outcomes but limited the ability to perform several other analyses. The significant findings in spite of the small number of persons in this category for a variety of hospitalization outcomes including death in the hospital, average length of stay per hospitalization, and average number of days in the hospital per year provide evidence of a strong effect of this measure of iron stores. Members of the cohort who joined an HMO before the end of the study further limited the number of subjects for follow-up because no claims data from this source of care were available for analysis. Furthermore, the CMS data covered care beginning in January 1, 1991, which meant that persons whose MEC visit was in 1988–1990 had missing data for hospitalizations that occurred between their MEC visit and this date, but because NDI mortality data were available for 1988–1990, information regarding their vital status during this period was available.

In conclusion, high TS is associated with greater mortality during hospitalizations and longer length of stay. Further studies to evaluate the clinical significance of these findings and develop possible interventions are needed.

ACKNOWLEDGMENTS

Funded in part by a cooperative agreement (MM1144) from the CDC.

Sponsor's Role: The funding agency played no part in the study, design, and concept of this manuscript.

REFERENCES

1. Edwards CQ, Kushner JP. Screening for hemochromatosis. N Engl J Med. 1993; 328:1616–1620. [PubMed: 8110209]
2. Pippard MJ. Detection of iron overload. Lancet. 1997; 349:73–74. [PubMed: 8996414]
3. Schmitt B, Golub RM, Green R. Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: Systematic review for the American College of Physicians. Ann Intern Med. 2005; 143:522–536. [PubMed: 16204165]
4. Qaseem A, Aronson M, Fitterman N, et al. Screening for hereditary hemochromatosis: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2005; 143:517–521. [PubMed: 16204164]

5. Iron Disorders Institute. Hemochromatosis diagnosis algorithm: Clinical evaluation and management protocol [on-line]. Available at http://www.irondisorders.org/Websites/idi/files/Content/854256/HHC%20ALL2011.pdf Accessed October 29, 2012
6. Mainous AG III, Gill JM, Carek PJ. Elevated transferrin saturation and mortality. Ann Fam Med. 2004; 2:133–138. [PubMed: 15083853]
7. Mainous AG III, Wells BJ, Carek PJ, et al. The mortality risk of elevated serum transferrin saturation and consumption of dietary iron. Ann Fam Med. 2004; 2:139–144. [PubMed: 15083854]
8. Mainous AG III, Gill JM, Everett CJ. Transferrin saturation, dietary iron intake, and risk of cancer. Ann Fam Med. 2005; 3:131–137. [PubMed: 15798039]
9. Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. Total mortality by transferrin saturation levels: Two general population studies and a meta analysis. Clin Chem. 2011; 57:459–466. [PubMed: 21228252]
10. Sempos CT, Looker AC, Gillum RF, et al. Body iron stores and risk of coronary disease. N Engl J Med. 1994; 330:1119–1124. [PubMed: 7993405]
11. Menke A, Muntner P, Fernandez-Real JM, et al. The association of biomarkers of iron status with mortality in US adults. Nutr Metab Cardiovasc Dis. 2012; 22:734–740. [PubMed: 21330119]
12. Looker AC, Johnson CL. Prevalence of elevated serum transferrin saturation in adults in the United States. Ann Intern Med. 1998; 129:940–945. [PubMed: 9867746]
13. National Digestive Diseases Information Clearinghouse (NDDIC): USDHHS. Hemochromatosis [on-line]. Available at http://digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/ Accessed October 29, 2011
14. Centers for Disease Control and Prevention. Hemochromatosis (iron storage disease): Training & education – treatment and management [on-line]. Available at http://www.cdc.gov/ncbddd/hemochromatosis/training/treatment/index.html Accessed October 29, 2012
15. Centers for Disease Control and Prevention. Surveillance for morbidity and mortality among older adults – United States, 1995–1996 [on-line]. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss4808a2.htm Accessed October 29, 2012
16. National Center for Health Statistics. Data access: NCHS Data linked to CMS Medicare enrollment and claims files [on-line]. Available at http://www.cdc.gov/nchs/data_access/data_linkage/cms_medicare.htm Accessed October 29, 2012
17. NHANES I Epidemiologic Follow-up Survey (NHEFS) calibration sample for NDI matching methodology. National Center for Health Statistics [on-line]. Available at http://www.cdc.gov/nchs/data/datalinkage/mort_calibration_study.pdf Accessed October 29, 2012
18. Schrier, SL. Mentzer, WC.; Stephen Landaw, A., editors. Causes and diagnosis of anemia due to iron deficiency in up to date 19.2. May 2011 [on-line]. Available at http://www.uptodate.com/contents/causes-and-diagnosis-of-anemia-due-to-iron-deficiency?source=preview&anchor=H13&selectedTitle=1~150#H13 Accessed October 29, 2012
19. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987; 40:373–383. [PubMed: 3558716]
20. American Diabetes Association (ADA). Summary of revisions for the 2010 clinical practice recommendations. Diabetes Care. 2010; 33(Suppl):S3. [PubMed: 20042773]
21. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003; 98:960–967. [PubMed: 12809815]
22. Molitch ME, DeFronzo RA, Franz MJ, et al. American Diabetes Association. Nephropathy in diabetes. Diabetes Care. 2004; 27(Suppl 1):S79–S83. [PubMed: 14693934]
23. Centers for Medicare and Medicaid. Medicare provider analysis and review (MEDPAR) file [on-line]. Available at https://www.cms.gov/IdentifiableDataFiles/05_MedicareProviderAnalysisandReviewFile.asp Accessed October 29, 2012
24. Graubard BI, Korn EL. Predictive margins with survey data. Biometrics. 1999; 55:652–659. [PubMed: 11318229]
25. Brissot P, Ropert M, Le Lan C, et al. Non-transferrin bound iron: A key role in iron overload and iron toxicity. Biochim Biophys Acta. 2012; 1820:403–410. [PubMed: 21855608]

26. Gaenzer H, Marschang P, Sturm W, et al. Iron stores and impaired endothelial function in patients with hereditary hemochromatosis. J Am Coll Cardiol. 2002; 40:2189–2194. [PubMed: 12505233]

27. Ellervik C, Mandrup-Poulsen T, Andersen HU, et al. Elevated transferrin saturation and risk of diabetes: Three population-based studies. Diabetes Care. 2011; 34:2256–2258. [PubMed: 21873562]

28. Agarwal R. Nonhematological benefits of iron. Am J Nephrol. 2007; 27:565–571. [PubMed: 17804903]

29. Anemia Fact Sheet. Iron Disorders Institute [on-line]. Available at http://www.irondisorders.org/Websites/idi/files/Content/854256/FActsAnemia.pdf Accessed October 29, 2012

30. Mukhopadhyay D, Mohanaruban K. Iron deficiency anaemia in older people: Investigation, management, and treatment. Age Ageing. 2002; 31:87–91. [PubMed: 11937470]

31. Mainous AG III, Diaz VA, Matheson EM, et al. Trends in hospitalizations with antibiotic-resistant infections: U.S., 1997–2006. Public Health Rep. 2011; 126:354–360. [PubMed: 21553664]

32. Mainous AG III, Diaz VA, Everett CJ, et al. Impact of insurance and hospital ownership on hospital length of stay among patients with ambulatory care sensitive conditions. Ann Fam Med. 2011; 9:489–495. [PubMed: 22084259]

Table 1

Baseline Demographic Characteristics of the Third National Health and Nutrition Examination Survey–Medicare Linked Cohort

Characteristic	Total	Men	Women	*P*-Value
Unweighted (N)	3,847	1,867	1,980	
Population estimate, n (%)	28,395,464	12,134,729 (42.7)	16,260,735 (57.3)	
Age,%				
65–74	61.4	66.6	57.6	<.001
≥75	38.6	33.4	42.4	
Race and ethnicity,%				
Non-Hispanic white	86.7	86.9	86.6	.84
Non-Hispanic black	7.5	7.2	7.7	
Hispanic	4.2	4.4	4.1	
Other	1.6	1.5	1.6	
Education,%				
<12th grade	43.5	45.5	42.1	<.001
High school	28.9	24.1	32.6	
>High school	27.5	30.4	25.4	
Charlson Comorbidity Index				
0	45.0	42.1	47.1	.069
1	18.7	21.0	17.0	
>2	36.3	36.9	35.9	
Transferrin saturation,%				
≥55.0	1.2	1.5	1.0	<.001
20.0–54.9	67.0	74.3	61.6	
<20.0	31.7	24.2	37.4	

Table 2

Most Frequent Primary Diagnoses for Hospitalization Episodes According to TS Level

≥55.0%	20.0–54.9%	<20.0%
Diagnosis (*International Classification of Diseases, Ninth Revision*, code)		
Ischemic heart disease (414)	Heart failure (428)	Heart failure (428)
Acute myocardial infarction (410)	Pneumonia (486)	Pneumonia (486)
Heart failure (428)	Cardiac dysrhythmia (427)	Acute myocardial infarction (410)
Pneumonia (486)	Ischemic heart disease (414)	Cardiac dysrhythmia (427)

Table 3

Logistic Regression for Risk of Death in the Hospital in Hospitalized Participants According to Transferrin Saturation Percentage

Transferrin Saturation, %	Odds Ratio (95% Confidence Interval)
>55	2.54 (1.05–6.12)
<20	1.31 (1.07–1.62)

Adjusted for age at baseline, sex, race and ethnicity, education, and Charlson Comorbidity Index.

Reference 20.0–54.9%.

Unweighted N = 3,048; weighted N = 22,559,000.

Table 4

Hospital Length of Stay Characteristics According to Transferrin Saturation Percentage Excluding Individuals Who Died in the Hospital

Transferrin Saturation (%)	Mean Days (Standard Error)	*P*-Value[a]
Average length of stay per hospitalization		
≥55.0	11.11 (±1.73)	.01
20.0–54.9	8.45 (±0.31)	Reference
<20.0	9.66 (±0.77)	.173
Average hospital days per year		
≥55.0	8.56 (±2.00)	.04
20.0–54.9	6.70 (±0.47)	Reference
<20.0	9.73 (±1.37)	.01
Average number of stays per year		
≥55.0	0.78 (±0.20)	.50
20.0–54.9	0.64 (±0.04)	Reference
<20.0	0.80 (±0.06)	.006

Adjusted for age at baseline, sex, race and ethnicity, education, and Charlson Comorbidity Index.

Unweighted N = 2,019; weighted N = 15,709,000.

[a] *P*-value based on difference in 1 n (days).