Chronic Kidney Disease in Patients with Chronic Liver Disease: What Is the Price Tag?

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The rising prevalence of chronic liver disease (CLD) in the United States contributes to significant increases in health care costs, driven primarily by increases in CLD-related hospitalizations from hepatic complications or decompensation.[1,2] Incidence of chronic kidney disease (CKD) has also increased due to the rising incidence of risk factors, such as diabetes and hypertension, in the general population. The contribution of CKD to the CLD-related clinical and economic burden is intriguing given the emerging association between CLD and the development of incident CKD, particularly among the nearly 90 million U.S. adults with nonalcoholic fatty liver disease (NAFLD). A recent study observed that NAFLD prevalence among veterans increased from 6.3% in 2003 to 17.6% in 2011 and that one in four U.S. adults in the general population has NAFLD.[3] In this issue of *Hepatology Communications*, Rustgi et al.[4] used a large, U.S.-based, real-world, commercial claims database (Truven Health MarketScan) from January 1, 2010, to December 31, 2015, to evaluate the health care resource utilization (HCRU) and cost burden associated with CKD in patients with underlying CLD. The investigators applied comprehensive algorithms based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) to accurately identify their CLD cohort, stratified by presence (n = 9,869) or absence (n = 588,586) of CKD, and further implemented 1:1 propensity score matching to ensure comparability of baseline demographics and comorbidities between the cohorts. When compared to patients with CLD but without CKD before matching, those with both CLD and CKD were older (mean age, 54.2 vs. 48.5 years), had a higher prevalence of diabetes (54.2% vs. 25.0%) and hypertension (90.3% vs. 51.9%), and had more advanced liver disease at baseline (decompensated cirrhosis, 27.2% vs. 11.8%). Interestingly, prevalence of presumably noncirrhotic NAFLD in the unmatched cohort was lower in patients with coexisting CKD (39.1% vs. 59.9%) when using a liberal definition for NAFLD (ICD-9-CM code of other chronic nonalcoholic liver disease in the absence of other CLD or excessive alcohol-use history). This was unexpected given the strong associations between NAFLD and metabolic diseases that have been hypothesized as a mechanism for NAFLD-related CKD.[5] It was also surprising to observe the low prevalence of alcoholic liver disease and the higher than expected prevalence of NAFLD in the study population when evaluating different etiologies of (presumably noncirrhotic) CLD. Part of this difficulty in accurately identifying liver disease etiologies reflects the challenges of using claims-based data sets, particularly for disease states without

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CLD, chronic liver disease; HCRU, health care resource use; HCV, hepatitis C virus; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NAFLD, nonalcoholic fatty liver disease.

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Robert J. Wong, M.D., M.S.
Division of Gastroenterology and Hepatology
Veterans Affairs Palo Alto Health Care System
3801 Miranda Avenue
Palo Alto, CA 94304
E-mail: rwong123@stanford.edu
Tel.: +1-650-493-5000 x63179

a defining biomarker, unlike chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV). Another possible explanation is that patients with CLD with cirrhosis, particularly those with decompensated cirrhosis, may have had a disproportionately higher burden of alcoholic liver disease and chronic HCV whereas those without cirrhosis or decompensated liver disease were largely represented by patients with NAFLD. Unfortunately, the current study did not separate the etiology from severity of liver disease, and thus it is unclear what the distribution of CLD etiologies was among the cohort of patients with liver transplant, liver cancer, and compensated and decompensated cirrhosis; together these represented 42% of the matched cohort. This lack of disease etiology stratification among patients with CLD with more advanced disease combined with the aforementioned challenges of a claims-based assessment of etiology may have contributed to some misclassification bias and may have skewed the proportion of patients categorized as NAFLD because many patients with NAFLD have mild liver disease.

In their propensity-matched cohort analysis, patients with CLD with CKD had significantly higher annual per-person all-cause health care costs compared to patients with CLD but without CKD ($21,397 vs. $16,995; $P < 0.0001$); this was primarily driven by increased use of outpatient visits as well as inpatient hospitalizations. The impact of co-existing CKD on HCRU and costs was even greater for patients with CLD with advanced liver disease, contributing to an excess unadjusted cost burden of $28,130 for patients with compensated cirrhosis, $47,090 for patients with decompensated cirrhosis, but surprisingly only $10,062 for patients with NAFLD, which was lower than that observed for patients with HBV or HCV. These observations add to existing literature highlighting the significant clinical and economic impact of CKD in patients with CLD. Much of the literature has focused on HCV cohorts, which not only demonstrated associations between HCV and the development of CKD and end-stage renal disease but also higher HCRU and costs associated with concurrent CKD in HCV cohorts. For example, Solid et al.[6] used both Truven Health MarketScan and U.S. Medicare fee-for-service 20% sample databases and observed that patients with HCV with CKD had a significantly higher prevalence of comorbidities (e.g., heart failure, stroke, pneumonia, sepsis, severe anemia, depression) and had significantly greater use of inpatient and outpatient services, which translated into higher total health care costs. A more recent study focusing on cirrhosis and in-hospital outcomes used 2004-2016 National Inpatient Sample data that included over 3.6 million cirrhosis-related hospitalizations.[7] Prevalence of acute kidney injury (AKI) among patients hospitalized with cirrhosis doubled from 15% in 2004 to 30% in 2016; this is particularly alarming given that the presence of AKI was associated with nearly 4 times greater odds of in-hospital death and 62% higher hospitalization costs. In a study among patients with cirrhosis who survived an episode of AKI, a quarter developed CKD and had more frequent bacterial infection and hospital readmission compared to those without CKD.[8]

The increasing prevalence of CKD in patients with CLD may also reflect convergence of two important epidemiologic patterns among U.S. adults: continued rising prevalence of metabolic diseases,[9] especially with an aging overall population and an aging CLD cohort, and rising prevalence of NAFLD as the major contributor to CLD burden[2] (Fig. 1). The rising prevalence of metabolic diseases, particularly hypertension and diabetes, is a major driver of both CKD and NAFLD, which along with emerging evidence suggesting NAFLD further contributes to CKD risk through proinflammatory or prothrombotic factors leading to vascular and renal damage,[5] may partly explain the increasing burden of CKD in patients with CLD. While it is no surprise that patients with CLD with CKD incurred higher health care costs than those without CKD, the current study adds to existing literature by providing important estimates of the actual dollar amounts and sources associated with this increased burden; this may be particularly important for payers and policy makers from a public health perspective.

These observations, however, should be interpreted with caution given the challenges of determining causation even in the most well-designed observational studies. Furthermore, it is often difficult to determine whether coexisting CKD was prevalent before development of CLD, which would, like most existing comorbidities, contribute to overall greater HCRU, costs, and perhaps even mortality, or whether incident CKD developed as a result of CLD. Whether the chicken or egg came first may not be critical insofar as understanding its impact on HCRU and costs for patients with CLD and concurrent CKD. It is also well-known that assessment of renal function in patients with cirrhosis using

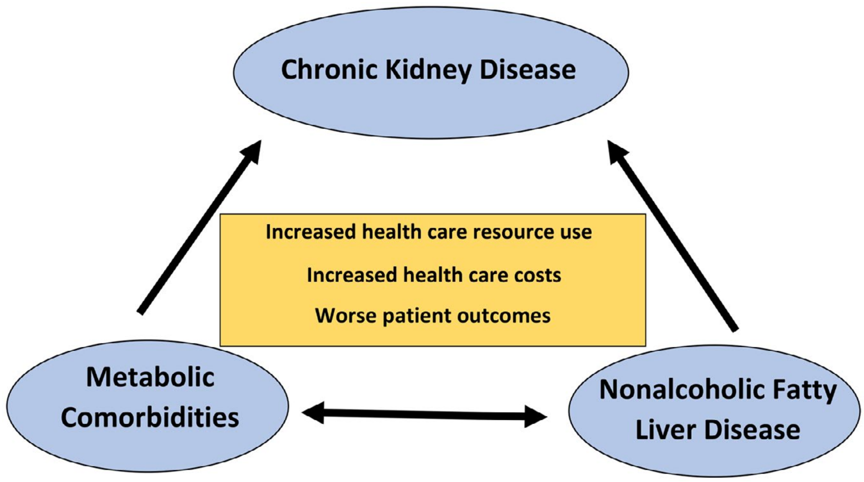

FIG. 1. The synergy of metabolic disorders, NAFLD, and CKD affects health care resource use and costs.

estimated glomerular filtration rate alone may be less accurate than using similar methods for patients without cirrhosis. As with any claims database, there is always a concern about accuracy of ICD-9-CM codes, as previously described, especially for diagnosis of NAFLD. Nevertheless, understanding potentially modifiable risk factors for incident CKD in patients with CLD may provide an opportunity for early risk identification and implementation of targeted prevention or therapies to reduce long-term risk of developing kidney injury. This would not only lead to significant health care costs savings but also improve patient outcomes. While the current study is an important call to raise greater awareness of the clinical and economic impact of CKD on patients with CLD, the patient and societal impacts in the real world are even greater when accounting for indirect costs (i.e., work absenteeism, decreased work productivity) and patient-reported quality of life.

Robert J. Wong, M.D., M.S. [1,2]
Ramsey C. Cheung, M.D. [1,2]
[1]**Division of Gastroenterology and Hepatology**
Veterans Affairs Palo Alto Health Care System
Palo Alto, CA
[2]**Division of Gastroenterology and Hepatology**
Stanford University School of Medicine
Stanford, CA

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