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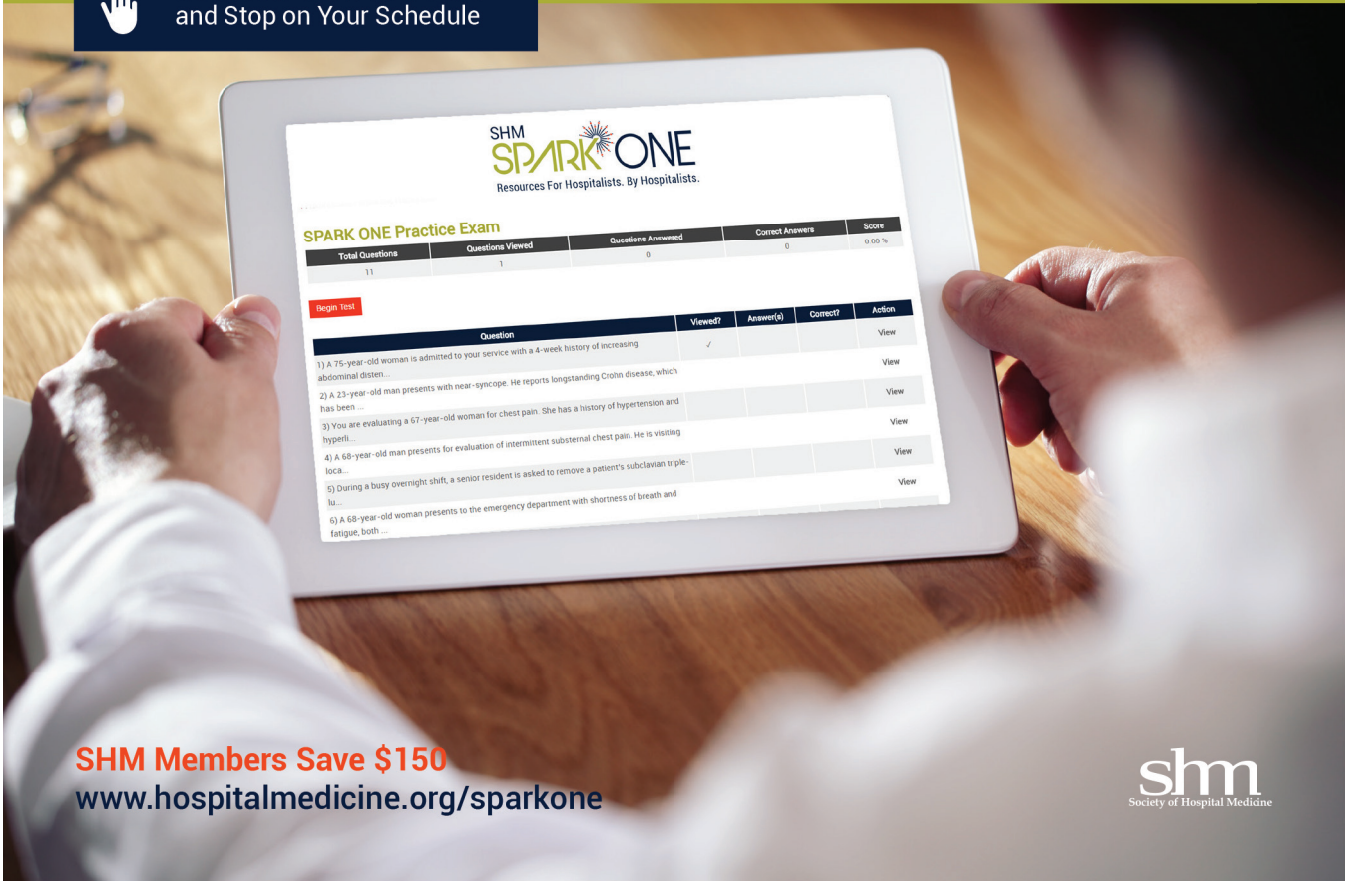

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WEBSITE
www.journalofhospitalmedicine.com

EDITORIAL STAFF
Editor
Jeff Bauer
(973) 206-2321
jbauer@frontlinemedcom.com

ART
Creative Director
Mary Ellen Niatas

Art Director
John J. DeNapoli

PRODUCTION AND MANUFACTURING
Production Manager
Mike Wendt
(973) 206-8010
mwendt@frontlinemedcom.com

CIRCULATION
Subscription Service:
(800) 480-4851
frontline@emscirc.com

PUBLISHING STAFF
Publisher
Mark Branca
(973) 290-8246
mbranca@frontlinemedcom.com

Director, Business Development
Angela Labrozzi, MBA
(973) 206-8971
Cell (917) 455-6071
alabrozzi@frontlinemedcom.com

Classified Sales
Linda Wilson
(973) 290-8243
lwilson@frontlinemedcom.com
Heather Gentile
(973) 290-8259
hgentile@frontlinemedcom.com

Accounts Receivable
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(973) 290-8211
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Cost of Acute Kidney Injury in Hospitalized Patients

Samuel A. Silver, MD, MSc[1,2*], Jin Long, PhD[1], Yuanchao Zheng, MS[1], Glenn M. Chertow, MD, MPH[1]

[1]Division of Nephrology, Stanford University School of Medicine, Palo Alto, California; [2]Division of Nephrology, University of Toronto, Toronto, Canada.

BACKGROUND: The economic burden of acute kidney injury (AKI) is not well understood.

OBJECTIVE: To estimate the effects of AKI on hospitalization costs and length of stay (LOS).

DESIGN: Using data from the 2012 National Inpatient Sample, we compared hospitalization costs and LOS with and without AKI. We used a generalized linear model with a gamma distribution and a log link fitted to AKI to adjust for demographics, hospital differences, and comorbidities.

SETTING: United States

PATIENTS: 29,763,649 adult hospitalizations without end-stage renal disease.

EXPOSURE: AKI determined using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes.

MEASUREMENTS: Hospitalization costs and LOS.

RESULTS: AKI was associated with an increase in hospitalization costs of $7933 (95% confidence interval [CI], $7608-$8258) and an increase in LOS of 3.2 (95% CI, 3.2-3.3) days compared to patients without AKI. When adjusted for patient and hospital characteristics, the associated increase in costs was $1795 (95% CI, $1692-$1899) and in LOS, it was 1.1 (95% CI, 1.1-1.1) days. Corresponding results among patients hospitalized with AKI requiring dialysis were $42,077 (95% CI, $39,820-$44,335) and 11.5 (95% CI, 11.2-11.8) days and $11,016 (95% CI, $10,468-$11,564) and 3.9 (95% CI, 3.8-4.1) days. AKI was associated with higher hospitalization costs than myocardial infarction and gastrointestinal bleeding, and costs were comparable to those for stroke, pancreatitis, and pneumonia.

CONCLUSIONS: In the United States, AKI is associated with excess hospitalization costs and prolonged LOS. The economic burden of AKI warrants further attention from hospitals and policymakers to enhance processes of care and develop novel treatment strategies. *Journal of Hospital Medicine* 2017;12:70-76. © 2017 Society of Hospital Medicine

Acute kidney injury (AKI) is a common complication that affects as many as 20% of hospitalized patients, depending on the definition employed.[1-3] AKI is associated with significant morbidity and mortality; hospitalized patients with AKI require more investigations and medications,[4] develop more postoperative complications,[5] and spend more time in the intensive care unit than do patients without AKI.[6] Inhospital mortality for patients with AKI has recently been estimated between 20-25%,[3,7] and critically ill patients with AKI requiring dialysis experience mortality rates in excess of 50%.[8,9] AKI and its accompanying complications may continue to rise, as the incidence of AKI and AKI requiring dialysis is increasing at a rate of approximately 10% per year.[10-12]

Owing to poor outcomes and rising incidence, AKI has emerged as a major public health concern with high human and financial costs; however, the costs related to AKI have been excluded from recent United States Renal Data System estimates.[13] Most studies that have explored the costs related to hospitalizations complicated by AKI have been single-center or local studies in specialized patient populations.[4,5,14-18] Very few studies have used data after the year 2000, when the incidence of AKI began to increase, likely related to a combination of patient age, comorbidity burden, sepsis, heart failure, and nephrotoxic medications.[10,11] Moreover, it is unclear which patient and hospital characteristics contribute most to the cost of an AKI hospitalization, and how the costs of AKI compare to those for other acute medical conditions. Such information is important for hospitals, policymakers, and researchers to target prevention and management strategies for high-risk and high-cost patient groups.

The main objectives of this study were to determine the costs of AKI-related hospitalization, and patient and hospital factors associated with these costs. We hypothesized that costs related to AKI would add several thousand dollars to each hospitalization and would eclipse the cost of many higher profile acute medical conditions.

METHODS

Study Population

We extracted data from the National Inpatient Sample (NIS), a nationally representative administrative database of hospitalizations in the United States (U.S.) created by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project.[19] The NIS is the largest all-payer inpatient-care database, and contains a 20% stratified sample of yearly discharge data from short-term, non-Federal, nonrehabilitation hospitals. Data are

***Address for correspondence and reprint requests**: Samuel A. Silver, Stanford University School of Medicine, Division of Nephrology, 1070 Arastradero Road, Palo Alto, CA, 94304; Telephone: 650-504-0030; Fax: 650-721-1443; E-mail: sam.silver@utoronto.ca

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stratified according to geographic region, location (urban/rural), teaching status, ownership, and hospital bed number. Each hospitalization is treated as an individual entry in the database (ie, individual patients who are hospitalized multiple times may be present in the NIS multiple times). The NIS includes demographic variables, diagnoses, procedures, LOS, and hospital charges. Sample weights are provided to allow for the generation of national estimates, along with information necessary to calculate the variance of estimates.

We utilized the 2012 NIS subset, the most recent year available at the time of data analysis. The 2012 NIS subset contained administrative data from over 7 million hospitalizations, representing more than 4000 hospitals, 44 states, and 95% of the US population. We excluded patients under 18 years of age and patients with end-stage renal disease (ESRD). We identified patients with ESRD using diagnosis codes and procedure codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, Supplemental Table 1). We also excluded hospitalizations with an ICD-9 diagnosis or procedure code for dialysis but without a diagnosis code for AKI, assuming that these patients were treated with dialysis for ESRD. We and others have used this approach,[11,20,21] which has been shown to produce high sensitivity and specificity, as well as high positive and negative predictive values (all equal to or greater than 90%) for differentiating dialysis-requiring AKI (AKI-D) from chronic dialysis.[21]

Primary and Secondary Exposures

Episodes of AKI were identified using the ICD-9 diagnosis code 584.x. This administrative code for AKI has low sensitivity, but high specificity of approximately 99%: our cohort includes few false positives, and identifies a more severe spectrum of AKI compared to serum creatinine criteria.[21,22] For example, the median (25^{th}, 75^{th} percentile) change in serum creatinine from baseline is estimated at 1.2 (0.7 to 2.1) mg/dL compared with 0.2 (0.1 to 0.2) mg/dL for patients without an administrative code for AKI.[21] We defined AKI-D as the presence of an AKI diagnosis code and a diagnosis or procedure code for dialysis. This algorithm for AKI-D has been shown to yield high sensitivity and specificity.[21] Secondary exposures included several acute medical conditions (myocardial infarction, stroke, venous thromboembolic disease, gastrointestinal bleed, acute pancreatitis, sepsis, and pneumonia) whose incremental costs and LOS could be compared to AKI (Supplemental Table 1).

Covariates

We assessed patient comorbidities from the 25 diagnoses listed in the NIS for each record (Supplemental Table 1). Hospital-level variables included geographic region, bed number, and teaching status using predetermined NIS definitions.[19]

Outcomes

The primary outcome was the inpatient cost of each hospital record in 2012 dollars. We estimated costs from the total

TABLE 1. Characteristics of the Cohort

Characteristic, %	No AKI (n = 26,732,623)	AKI[a] (n = 3,031,026)	AKI-D (n = 106,515)
Age, mean (SD)	55.8 (0.1)	69.0 (0.1)	63.3 (0.2)
Sex			
Male	38.9%	52.8%	58.2%
Female	61.1%	47.3%	41.8%
Hospital teaching status			
Rural	12.1%	9.8%	5.2%
Urban nonteaching	38.7%	38.8%	37.0%
Urban teaching	49.2%	51.4%	57.8%
Hospital region			
Northeast	19.7%	18.8%	16.1%
West	18.9%	18.4%	21.3%
Midwest	22.9%	22.7%	22.4%
South	38.5%	40.1%	40.2%
Hospital bed number			
Small	14.5%	12.8%	9.2%
Medium	26.5%	26.5%	24.2%
Large	59.1%	60.7%	66.7%
Acute medical conditions			
Myocardial infarction	2.6%	6.7%	11.0%
Stroke	3.0%	3.4%	4.1%
Venous thromboembolic disease	2.1%	3.9%	7.3%
Gastrointestinal bleed	2.2%	5.3%	8.9%
Acute pancreatitis	1.3%	1.9%	4.4%
Sepsis	3.6%	20.2%	43.0%
Pneumonia	6.6%	16.1%	27.0%
Chronic comorbidities			
Cancer	9.0%	12.7%	14.7%
Chronic kidney disease	7.1%	46.2%	51.3%
Congestive heart failure	11.8%	34.0%	40.5%
Dementia	5.4%	11.9%	3.7%
Diabetes	21.3%	41.6%	41.2%
Human immunodeficiency virus	0.3%	0.7%	1.0%
Hypertension	47.4%	73.0%	66.0%
Chronic obstructive pulmonary disease	12.7%	20.0%	18.0%
Peripheral vascular disease	5.4%	10.8%	11.6%
Hospital procedures			
Intravenous contrast	4.9%	5.4%	8.7%
Blood product transfusion	6.8%	17.8%	40.8%
Mechanical ventilation	2.2%	11.2%	43.4%
Noninvasive ventilation	1.5%	4.2%	8.0%
Cardiopulmonary resuscitation	0.2%	1.3%	5.6%
Left ventricular assist device	0.0%	0.1%	0.5%
Extracorporeal membrane oxygenation	0.0%	0.1%	0.4%
Echocardiogram	2.3%	4.7%	8.0%
Coronary angiogram	4.1%	4.7%	7.7%
Percutaneous transluminal coronary angioplasty	1.8%	1.4%	2.0%
Cardiopulmonary bypass	0.8%	1.3%	3.7%
Coronary artery bypass grafting	0.6%	1.1%	2.3%
Heart valve surgery	0.3%	0.7%	2.1%
Abdominal aortic aneurysm repair	0.2%	0.2%	0.8%
Carotid endarterectomy	0.4%	0.1%	0.2%
Peripheral vascular surgery	0.6%	0.8%	1.7%

[a]The AKI group includes patients with AKI-D.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis.

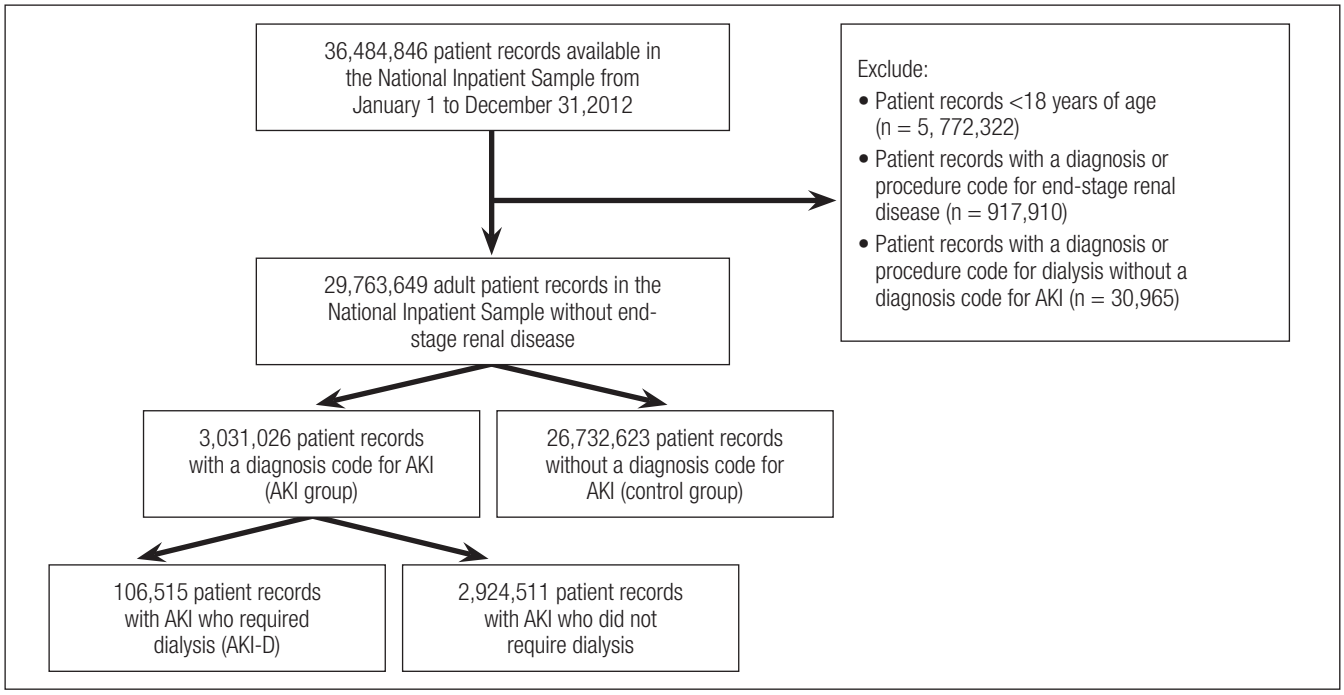

FIG. 1. Inclusion and exclusion criteria used to define a cohort of patients with and without AKI
NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis.

charge for each hospitalization by applying hospital-specific charge-to-cost ratios. The NIS obtained cost information from the hospital accounting reports collected by the Centers for Medicare and Medicaid Services.[19] The secondary outcome was hospital LOS.

Statistical Analysis

We summarized baseline characteristics of the study participants using descriptive statistics. Normally distributed continuous variables were expressed as mean (standard deviation [SD]), and nonparametric continuous variables were expressed as median (25th, 75th percentile). Categorical variables were expressed as proportions. We calculated the mean increase in cost and LOS of each hospital record, comparing hospital records with AKI and AKI-D to hospital records without AKI. We took the same approach when examining incremental costs and LOS associated with other acute medical conditions. Due to the skewness of cost and LOS data, we used a generalized linear model with a gamma distribution and a log link fitted to the primary or secondary exposure to obtain the unadjusted mean increase in cost and LOS.[23,24] We incorporated demographics, hospital differences, comorbidities (including AKI when it was compared to the other acute medical conditions), and procedures into the generalized linear model to calculate the adjusted mean increase in cost and LOS. This method also provides the adjusted percentage change in hospital costs and LOS from the estimated beta-coefficients in the multivariable model. We calculated the proportion of variation in the outcomes explained by the generalized linear models using pseudo R-squared measured by the Kullback-Leibler divergence.[25] As a companion analysis, we repeated estimates for AKI-D when dialysis was initiated within 7 days of hospital admission because subsequent events during the hospital stay would more likely be attributable to the AKI episode. All analyses presented account for the NIS survey design (weighting and stratification) and subpopulation measurements to generate national estimates. We created the cohort using the Statistical Analysis System software, version 9.4 (SAS Institute, Cary, North Carolina) and conducted the analyses using StataMP, version 14.0 (Stata Corporation, College Station, Texas).

RESULTS

Patient Characteristics

Between January 1 and December 31, 2012, there were 36,484,846 hospitalization records available in the NIS; 948,875 adult records (2.6%) were classified as having ESRD and 29,763,649 (81.6%) were included in the final cohort. Within the final cohort, 3,031,026 (10.2%) hospitalizations were complicated by AKI, of which 106,515 (3.5%) required dialysis (corresponding to 0.36% of the analytic cohort) (Figure 1).

Compared to patients without AKI, patients with AKI were older (69.0 years vs. 55.8 years) and a larger proportion were male (52.8% vs. 38.9%). All measured comorbidities were more prevalent in patients with AKI. Patients with AKI also underwent more hospital procedures than patients without AKI (Table 1).

Hospitalization Costs

Figures 2A and 2B show unadjusted and multivariable-adjusted mean increases in cost of a hospitalization with AKI

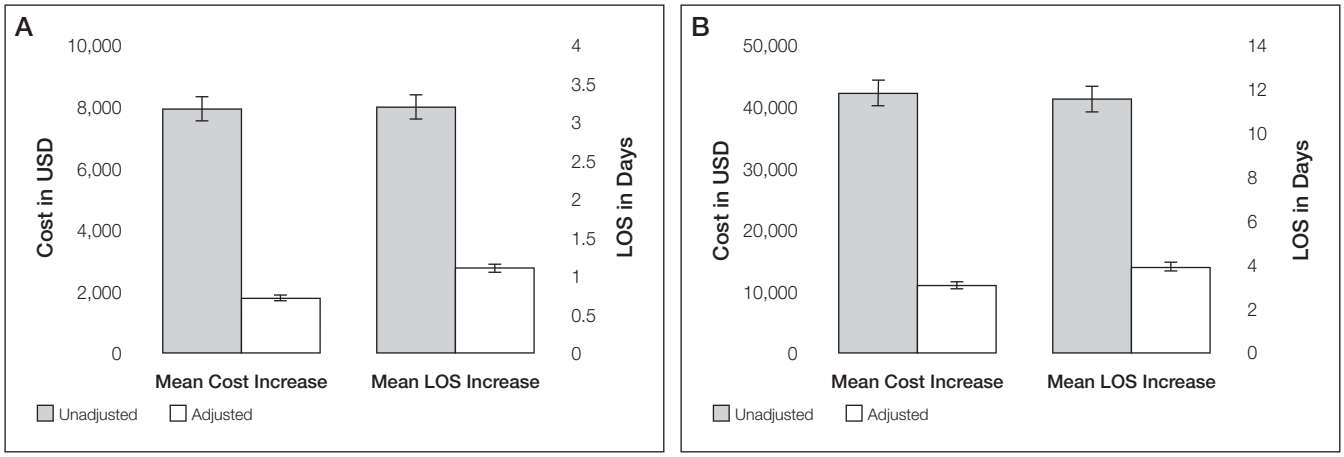

FIG. 2. (A) Mean increase in cost and LOS per hospital admission of AKI compared to a hospital admission without AKI. Costs increases are in 2012 dollars. White bars are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Error bars represent the 95% confidence intervals. The multivariable model explained 67% of the variation in total hospital costs and 47% of the variation in LOS. (B) Mean increase in cost and LOS per hospital admission of AKI-D compared to a hospital admission without AKI. Cost increases are in 2012 dollars. White bars are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Error bars represent the 95% confidence intervals. The multivariable model explained 53% of the variation in total hospital costs and 64% of the variation in LOS.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; LOS, length of stay.

and AKI-D compared to a hospitalization without AKI. Extrapolating to the 2012 population estimates in Table 1 for AKI and AKI-D, increases in cost related to AKI ranged from $24.0 billion (unadjusted) to $5.4 billion (adjusted) and for AKI-D ranged from $4.5 billion (unadjusted) to $1.2 billion (adjusted).

Mean increases in the cost of a hospitalization for AKI exceeded costs associated with other acute medical conditions such as myocardial infarction and gastrointestinal bleeding. Costs associated with AKI were similar to hospitalizations for stroke, acute pancreatitis, and pneumonia. Costs of AKI-D exceeded those related to sepsis and venous thromboembolic disease (Table 2). AKI was the most common of the acute medical conditions examined (3,031,026 patients, 10.2%).

Major drivers of cost included urban and teaching hospitals, hospitals in the Southern US (relative to other regions), hospitals with a larger number of beds, most acute medical conditions, cancer, and hospital procedures. Older age was associated with higher costs with non-AKI hospitalizations but lower costs with AKI hospitalizations (0.67% vs. -0.44%, per year of age). Determinants of hospital costs are shown in Supplemental Table 2. Generally, hospital procedures accounted for the largest relative increases in cost.

Length of Stay

Figures 2A and 2B show unadjusted and multivariable-adjusted mean increases in LOS for a hospitalization with AKI and AKI-D compared to a hospitalization without AKI. Extrapolating to the 2012 population estimates in Table 1 for AKI and AKI-D, increases in LOS related to AKI ranged

TABLE 2. Mean Increase in Cost and LOS per Hospital Admission of AKI and Other Acute Medical Conditions

Acute Medical Condition	Prevalence, No. (%)	Adjusted Mean Cost Increase in 2012 US Dollars (95% CI)[a]	Adjusted Mean Length of Stay Increase in Days (95% CI)[a]
AKI[b]	3,031,026 (10.2)	1795 (1692, 1899)	1.1 (1.1, 1.1)
AKI requiring dialysis (AKI-D)	106,515 (0.4)	11016 (10468, 11564)	3.9 (3.8,4.1)
Myocardial infarction	901,276 (3.0)	14 (-91, 119)	0.1 (0.1, 0.2)
Stroke	901,227 (3.0)	1427 (1281,1573)	0.1 (0, 0.1)
Venous thromboembolic disease	677,202 (2.3)	3782 (3611, 3953)	2.3 (2.2, 2.3)
Gastrointestinal bleed	743,692 (2.5)	-860 (-961, -759)	0 (0, 0.1)
Acute pancreatitis	413,827 (1.4)	1802 (1676,1929)	1.1 (1.1, 1.2)
Sepsis	1,577,242 (5.3)	4882 (4696, 5068)	2.1 (2.1, 2.2)
Pneumonia	2,246,687 (7.5)	1705 (1584,1825)	1.2 (1.2, 1.2)

[a]For each comparison, the reference group is patients without the condition of interest (for AKI-D, the reference group is patients without AKI). All estimates are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Non-AKI conditions are also adjusted for AKI.

[b]The AKI group includes patients with AKI-D.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; CI, confidence interval; LOS, length of stay.

from 9.8 million days (unadjusted) to 3.3 million days (adjusted) and for AKI-D ranged from 1.2 million days (unadjusted) to 0.4 million days (adjusted).

When compared to other acute medical conditions, the mean increase in LOS of an AKI hospitalization resembled the order for mean increases in cost (Table 2). Major drivers of LOS also resembled drivers of costs, with the exception of some common cardiovascular procedures (percutaneous transluminal coronary angioplasty, abdominal aortic aneurysm repair, and carotid endarterectomy) that were associated only with prolonged LOS in the AKI and AKI-D groups (Supplemental Table 3).

Companion Analysis

In an analysis of 78,220 patients who developed AKI-D within 7 days of hospital admission (73% of AKI-D cases), increases in cost ranged from $32,133 (unadjusted) to $8594 (adjusted) and increases in LOS ranged from 8.4 days (unadjusted) to 2.9 days (adjusted) compared to patients without AKI.

DISCUSSION

We found that hospitalizations complicated by AKI were more costly—between $1800 and $7900—than hospitalizations that did not involve AKI, which indicates that AKI could be responsible for billions of dollars of annual healthcare spending. Relative to several other acute medical conditions, AKI was more common and expensive; when AKI was severe enough to require dialysis, costs of AKI exceeded all other acute medical conditions by a large margin.

Several single-center and regional studies have highlighted the association of AKI with hospital costs and LOS. In a single-center study conducted in the late 1990s, Chertow et al[14] described mean cost increases between $4900 (adjusted) and $8900 (unadjusted) and LOS increases of 3.5 days (adjusted) using serum creatinine criteria to define AKI.[14] These higher adjusted estimates may result because their multivariable models did not adjust for several major determinants of cost, including several procedures and hospital-level variables. A study at the same academic center in 2010, which adjusted for some procedures, found AKI was associated with a 2.8-day increase in LOS and a $7082 increase in costs;[2] however, this study also could not adjust for hospital-level variables because of the single-center design. Fischer et al[15] were able to adjust for hospital teaching status in their study that included 23 local hospitals. Similar to our results, teaching hospitals were associated with an approximately 17% increase in cost compared to nonacademic hospitals. However, this study excluded patients who required critical care or mechanical ventilation, which limits the generalizability of their cost estimates. Another limitation of these 3 studies is that they were all conducted in Massachusetts. Beyond the US, the economic burden of AKI has been studied in England where the annual cost of AKI-related inpatient care has been estimated at $1.4 billion.[16] In addition to incomplete procedure and hospital-level adjustment, this study is limited by its ascertainment of AKI and costs, which was extrapolated from 1 hospital region to the rest of England.

Our study adds to the existing evidence in a number of ways. It uses nationally representative data to determine a lower and an upper limit of increases in cost and LOS attributable to AKI. The adjusted value is likely overly conservative; it minimizes the influence of events that are attributable to AKI and does not account for complications that may be caused by, or otherwise related to, AKI. The unadjusted value is likely an overestimate, attributing events during an AKI hospitalization to the AKI episode, even if they precede AKI. In clinical practice, most patients fall between these 2 extremes. Therefore, we suggest using the adjusted and unadjusted estimates to provide a range of the cost and LOS increases that are attributable to AKI. This interpretation is also supported by the companion analysis that minimizes the effect of pre-AKI events, where the unadjusted cost and LOS estimates for AKI-D occurring early during a hospitalization fell between the unadjusted and adjusted estimates for the main AKI-D analysis. Therefore, our data suggest that each hospitalization complicated by AKI is associated with a cost increase between $1800 and $7900 and an LOS increase between 1.1 days and 3.2 days. Not surprisingly, the burden of AKI-D was more pronounced with a cost increase between $11,000 and $42,100 and an LOS increase between 3.9 days and 11.5 days.

Unlike previous studies, these analyses are fully adjusted for procedures and multiple hospital-level variables (such as teaching status, region, and bed number). These adjustments are important because procedures account for much of the incremental cost and LOS associated with AKI, and each hospital-level variable may increase the cost and LOS of an AKI hospitalization by 10% to 25% (Supplemental Tables 2 and 3). Even though the relative increases in cost and LOS associated with different comorbidities and procedures were largely similar between patients with and without AKI, the absolute increases were usually larger in patients with AKI rather than without AKI because of their higher baseline estimates. We also observed that each year of age was associated with increased costs in patients without AKI, but decreased costs in patients with AKI. We suspect this difference is due to the lesser (and ultimately less costly) injury required to induce AKI in elderly patients who have less physiologic reserve.[26] Moreover, we placed the burden of AKI in relation to other acute medical conditions, where its total estimated annual costs of $5.4 billion were exceeded only by the $7.7 billion attributed to sepsis.

Our results emphasize that AKI is an important contributor to hospital costs and LOS. Despite these consequences, there have been very few innovations in the prevention and management of AKI over the last decade.[27,28] The primary treatment for severe AKI remains dialysis, and recent clinical trials suggest that we may have reached a dose plateau in the value of dialytic therapy.[8,29] Several opportunities, such as advances in basic science and clinical care, may improve the care of patients with AKI. Translational research chal-

lenges in AKI have been reviewed, with treatment strategies that include hemodynamic, inflammatory, and regenerative mechanisms.[28, 30] In a recent report from the National Confidential Enquiry into Patient Outcome and Death in the United Kingdom, 30% of AKI episodes that occurred inhospital were preventable, and only 50% of patients with AKI were deemed to have received good care.[31] Our results suggest that even small progress in these areas could yield significant cost savings. One starting point suggested by our findings is a better understanding of the reasons underlying the association between hospital-level variables and differences in cost and LOS. Notably, there have been few efforts to improve AKI care processes on the same scale as sepsis,[32] myocardial infarction,[33,34] stroke,[35] and venous thromboembolic disease.[36]

Strengths of this study include cost and LOS estimates of AKI from different hospitals across the US, including academic and community institutions. As a result, our study is significantly larger and more representative of the US population than previously published studies. Moreover, we utilized data from 2012, which accounts for the increasing incidence of AKI and recent advances in critical care medicine. We were also able to adjust for comorbid conditions, procedures, severity of illness, and hospital-level variables, which provide a conservative lower limit of the burden of AKI on hospitalized patients.

Our study has limitations. First, we used administrative codes to identify patients with AKI. The low sensitivity of these codes suggests that many patients with milder forms of AKI were probably not coded as such. Accordingly, our findings should be generally applicable to patients with moderate to severe AKI rather than to those with mild AKI.[21,22] Second, the NIS lacks granularity on the details and sequence of events during a hospitalization. As a result, we could not determine the timing of an AKI episode during a hospitalization or whether a diagnosis or procedure was the cause or consequence of an AKI episode (ie, day 1 as the reason for admission vs. day 20 as a complication of surgery). Both the timing and cause of an AKI episode may influence cost and LOS, which should be considered when applying our results to patient care. We did not attempt to estimate the costs associated with comorbidities such as congestive heart failure and chronic obstructive pulmonary disease because we could not determine the acuity of disease in the NIS. Third, despite our efforts, residual confounding is likely, especially since administrative data limit our ability to capture the severity of comorbid conditions and the underlying illness. Fourth, the NIS does not contain individual patient identifiers, so multiple hospitalizations from the same patient may be represented.

Even our most conservative estimates still attribute $5.4 billion and 3.3 million hospital-days to AKI in 2012. These findings highlight the need for hospitals, policymakers, and researchers to recognize the economic burden of AKI. Future work should focus on understanding hospital-level differences in AKI care and the effect on patient morbidity and mortality. National and hospital-wide quality improvement programs are also needed. Such initiatives have commenced in the United Kingdom,[37] and similar efforts are needed in North America to develop and coordinate cost-effective strategies to care for patients with AKI.

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Acute Kidney Injury in Patients Treated with Vancomycin and Piperacillin-Tazobactam: A Retrospective Cohort Analysis

W. Cliff Rutter, PharmD[1,2,3], Donna R. Burgess, RPh[1,2], Jeffery C. Talbert, PhD[1,3,4], David S. Burgess, PharmD[1*]

[1]University of Kentucky College of Pharmacy, Lexington, Kentucky; [2]University of Kentucky HealthCare, Lexington, Kentucky; [3]University of Kentucky Institute for Pharmaceutical Outcomes and Policy, Lexington, Kentucky; [4]University of Kentucky Center for Clinical and Translational Science, Lexington, Kentucky.

BACKGROUND: Empiric antimicrobial therapy often consists of the combination of gram-positive coverage with vancomycin (VAN) and gram-negative coverage, specifically an antipseudomonal beta-lactam such as piperacillin-tazobactam (PTZ). Nephrotoxicity is commonly associated with VAN therapy; however, recent reports show higher nephrotoxicity rates among patients treated with the combination of VAN and PTZ.

OBJECTIVE: This study evaluated the effect of the VAN/PTZ combination on acute kidney injury (AKI) compared to VAN and PTZ monotherapies.

DESIGN, SETTING, AND PATIENTS: This is a retrospective cohort analysis of adult patients without renal disease receiving VAN, PTZ, or the combination from September 1, 2010 through August 31, 2014 at an academic medical center.

MEASUREMENTS: The primary outcome was AKI incidence as defined by the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria.

METHODS: Continuous and categorical variables were assessed with appropriate tests. Univariate and multivariate logistic regressions were performed to assess for associations between variables and AKI incidence. Subanalyses based on severity of illness were performed.

RESULTS: Overall, 11,650 patients were analyzed, with 1647 (14.1%) developing AKI. AKI was significantly more frequent in the VAN/PTZ group (21%) compared to either monotherapy group (VAN 8.3%, PTZ 7.8%, $P < 0.001$ for both). Combination therapy was independently associated with higher AKI odds compared to monotherapy with either agent (adjusted odds ratio [aOR], 2.03; 95% confidence interval [CI], 1.74-2.39; aOR, 2.31; 95% CI, 1.97-2.71, for VAN and PTZ, respectively). Receipt of concomitant nephrotoxic drugs was independently associated with increased AKI rates, as were increased duration of therapy, hospital length of stay, increasing severity of illness, and increasing baseline renal function.

CONCLUSIONS: In this study of more than 10,000 patients, VAN combined with PTZ was associated with twice the odds of AKI development compared to either agent as monotherapy. This demonstrates the need for judicious use of combination empiric therapy. *Journal of Hospital Medicine* 2017;12:77-82. © 2017 Society of Hospital Medicine

Empiric antimicrobial therapy often consists of the combination of gram-positive coverage with vancomycin (VAN) and gram-negative coverage, specifically an antipseudomonal beta-lactam such as piperacillin-tazobactam (PTZ). Literature from a variety of patient populations reports nephrotoxicity associated with VAN, targeting troughs greater than 15 µg/mL, that occur in 5% to 43% of patients.[1] In a study of critically ill patients, acute kidney injury (AKI) was found in 21% of patients receiving VAN, with increasing duration of VAN treatment, greater VAN levels, concomitant vasoactive medication administration, and intermittent infusion methods being associated with higher odds of AKI.[2] A recent report from adult internal medicine patients estimated the incidence of VAN-associated nephrotoxicity at 13.6% and implicated concomitant PTZ therapy as a key factor in these patients.[3]

Further studies have explored the interaction between empiric beta-lactam and VAN therapy, showing mixed results. Reports of AKI associated with the combination of VAN and PTZ range from 16.3% to 34.8%,[4-8] while the cefepime-VAN combination is reported to range from 12.5% to 13.3%.[5,6] While VAN monotherapy groups were well represented, only 1 study[7] compared the PTZ-VAN combination to a control group of PTZ monotherapy.

The primary objective of this study was to evaluate the differences in AKI incidence between patients treated with VAN and with PTZ, alone and in combination.

METHODS

This is a retrospective cohort study of adult patients conducted at the University of Kentucky Chandler Medical Center (UKMC) from September 1, 2010 through August 31, 2014. Patients were included if they were at least 18 years of age on admission; remained hospitalized for at least 48 hours; received VAN combined with PTZ (VAN/PTZ), VAN alone, or PTZ alone; and had at least 48 hours of therapy (and 48 hours of overlapping therapy in the VAN/PTZ group). Patients were excluded if they had underlying diagnosis of chronic kidney disease according to the International Classification of Diseases 9 (ICD-9) code, were re-

***Address for correspondence and reprint requests:** David S. Burgess, PharmD, FCCP, University of Kentucky College of Pharmacy, 789 South Limestone Street, TODD 292K, Lexington, KY 40536-0596; Telephone: 859-218-0948; Fax: 859 323-0069; E-mail: david.burgess@uky.edu

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ceiving renal replacement therapy before admission, had a diagnosis of cystic fibrosis, or were pregnant. Additionally, patients were excluded if they presented with AKI, defined as an initial creatinine clearance less than 30 mL/min, or if baseline creatinine clearance was greater than 4 times the standard deviation from the mean; serum creatinine values were not obtained during admission; and if AKI occurred prior to therapy initiation, within 48 hours of initiation, or more than 7 days after treatment was discontinued. Patients were followed throughout their stay until time of discharge.

Data Source

Patient data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT). The EDT contains clinical data from the inpatient population of UKMC from 2006 to present. Data stored and updated nightly by the EDT includes: demographics, financial classification (Medicare, Medicaid, private insurance), provider-level detail (service line), medical diagnosis (ICD-9 codes), medical procedures (Current Procedural Terminology [CPT] codes), lab tests and results, medication administration details, visit details (age, length of stay, etc), and vital signs. This study was approved by the UKMC Institutional Review Board.

Data collected for each patient included: demographic data, visit details (length of stay, admitting and primary diagnosis codes, etc.), severity of underlying illness as defined by the Charlson Comorbidity Index (CCI), all serum creatinine levels drawn per visit, medication administration information (dose, date, and time administered), all VAN trough levels, receipt of other nephrotoxic agents, blood pressures, and receipt of vasopressors.

Outcome Ascertainment

The definition of AKI was based on the RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria,[9] with risk defined as a 25% to 50% decrease in estimated glomerular filtration rate (GFR), injury as a 50% to 75% decrease in estimated GFR, and failure defined as a greater than 75% decrease in estimated GFR. Loss and end-stage classifications were not assessed because of this study's follow-up period. The adjusted Cockcroft and Gault equation[10] was used to estimate GFR due to the inconsistency of weight availability in the dataset and concordance with the institution's practice. Baseline creatinine clearance was calculated with the first serum creatinine obtained, and the minimum creatinine clearance was calculated using the maximum serum creatinine during each patient's visit. The percent decrease in creatinine clearance was calculated from these 2 values. AKI status was defined as meeting any of the RIFLE criteria. Mortality was assessed for all patients and defined as the composite of inhospital mortality and discharge or transfer to hospice care.

Exposure Ascertainment

Hypotension exposure was defined as experiencing 1 of the following: mean arterial blood pressure less than 60 mm Hg, a diagnosis of hypotension by a physician, or receipt of vasopressors or inotropic agents. Days of therapy for each drug were obtained and combination days of therapy were calculated by including only those days in which the patient received both medications. Total days of therapy were calculated by the sum of all days receiving at least 1 study agent. Exposure to other nephrotoxic agents (eg, acyclovir, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists, aminoglycosides, amphotericin B, cyclosporine, foscarnet, loop diuretics, nonsteroidal anti-inflammatory drugs, sulfonamides, tacrolimus, and tenofovir) were defined as receipt of at least 1 dose of the agent during hospitalization.

Statistical Analysis

Characteristics between groups were described with basic descriptive statistics. Continuous variables were compared with 1-way analysis of variance (ANOVA) or the Kruskal-Wallis test. Categorical variables were compared with chi-square or Fisher exact test. Yearly AKI trends were assessed with Pearson correlation coefficient. To control for differences in underlying severity of illness between groups, a subanalysis was performed in which the cohort was split into 4 groups (0, 1, 2 to 4, and ≥5 points) based on CCI. Univariate models for all covariates were created with probability of AKI as the outcome. Covariates significant after univariate were incorporated into the multivariate model, which was subsequently adjusted to achieve the highest predictive accuracy by minimizing the Akaike information criterion (AIC). Nephrotoxic agent exposures were included in the final multivariate model regardless of statistical significance in univariate analysis. Model fit was assessed with a standardized Hosmer-Lemeshow goodness-of-fit test.[11] All statistical analyses were completed with RStudio v 0.98 running R v 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).[12] All tests were 2-tailed and significance was defined at an alpha of 0.05.

RESULTS

Of 17,879 patients initially screened, 11,650 patients were evaluated, of which 5,497 received VAN and PTZ (VAN/PTZ), 3,055 received VAN alone, and 3,098 received PTZ alone. Table 1 contains basic demographic information. The mean age of patients was 52.5 years ± 16.8 years with 6,242 (53.6%) males. Patients receiving VAN/PTZ had higher CCIs than either monotherapy group and had significantly increased length of hospitalization. While patients in the combination therapy group were more likely to experience hypotension, concomitant nephrotoxic agent exposure was more common in the VAN monotherapy group.

RIFLE-defined AKI occurred in 1,647 (14.1%) across the entire cohort. AKI occurred in 21% of VAN/PTZ patients, 8.3% of VAN patients, and 7.8% of PTZ patients ($P < 0.0001$). RIFLE-defined risk, injury, and failure occurred more frequently in the VAN/PTZ cohort compared to the VAN and PTZ monotherapy groups (Figure). There were no

TABLE 1. Baseline Characteristics

Outcome	VAN	PTZ	VAN/PTZ	*P* value
	(n = 3055)	(n = 3098)	(n = 5497)	
Age (y) [mean (± SD)]	52.5 (16.9)	53.3 (17.5)	52.0 (16.3)	0.003
Age group (y)				<0.0001
18-29	333 (10.9%)	379 (12.2%)	594 (10.8%)	
30-49	940 (30.8%)	837 (27.0%)	1736 (31.6%)	
50-64	984 (32.2%)	1034 (33.4%)	1904 (34.6%)	
65-79	630 (20.6%)	632 (20.4%)	1019 (18.5%)	
≥80	168 (5.5%)	216 (7.0%)	244 (4.4%)	
Male gender	1462 (47.9%)	1523 (49.2%)	3257 (59.3%)	<0.0001
CCI [median (IQR)]	2 (0-4)	2 (0-5)	3 (1-5)	<0.0001
Baseline creatinine clearance (mL/min) [mean (±SD)]	100.9 (40.4)	100.1 (42.7)	101.9 (43.6)	0.2
CrCl group (mL/min)				<0.0001
30-59	394 (12.9%)	528 (17.0%)	855 (15.6%)	
60-89	984 (32.2%)	888 (28.7%)	1539 (28.0%)	
≥90	1677 (54.9%)	1682 (54.3%)	3103 (56.4%)	
Transfer from outside facility	646 (21.1%)	867 (28.0%)	1487 (27.1%)	<0.0001
Admission type				<0.0001
Elective	904 (29.6%)	398 (12.8%)	644 (11.7%)	
Emergency	1329 (43.5%)	1692 (54.6%)	2956 (53.8%)	
Trauma	102 (3.3%)	137 (4.4%)	524 (9.5%)	
Urgent	720 (23.6%)	871 (28.1%)	1373 (25.0%)	
Hypotension exposure	447 (14.6%)	442 (14.3%)	1560 (28.4%)	<0.0001
Dehydration diagnosis	98 (3.2%)	225 (7.3%)	312 (5.7%)	<0.0001
Length of stay (d) [median (IQR)]	5 (3-9)	5 (3-9)	7 (4-14)	<0.0001
Length of stay (d)				<0.0001
≤7	2084 (68.2%)	2144 (69.2%)	2760 (50.2%)	
8-14	596 (19.5%)	641 (20.7%)	1438 (26.2%)	
15-21	182 (6.0%)	179 (5.8%)	637 (11.6%)	
>21	193 (6.3%)	134 (4.3%)	662 (12.0%)	
Nephrotoxic agent exposure	1970 (64.5%)	1434 (46.3%)	3343 (60.8%)	<0.0001
Acyclovir	202 (6.6%)	19 (0.6%)	109 (2.0%)	<0.0001
ACE inhibitor	595 (19.5%)	545 (17.6%)	1142 (20.8%)	0.002
ARB	159 (5.2%)	133 (4.3%)	167 (3.0%)	<0.0001
Aminoglycoside	336 (11.0%)	126 (4.1%)	630 (11.5%)	<0.0001
Amphotericin B	30 (1.0%)	11 (0.4%)	78 (1.4%)	<0.0001
Contrast	165 (5.4%)	257 (8.3%)	418 (7.6%)	<0.0001
Cyclosporine	8 (0.3%)	12 (0.4%)	13 (0.2%)	0.4
Foscarnet	4 (0.1%)	1 (0.03%)	5 (0.1%)	0.4
Loop diuretic	594 (19.4%)	607 (19.6%)	1,828 (33.3%)	<0.0001
NSAID	874 (28.6%)	309 (10.0%)	752 (13.7%)	<0.0001
Sulfonamide	19 (0.6%)	18 (0.6%)	95 (1.7%)	<0.0001
Tacrolimus	34 (1.1%)	75 (2.4%)	108 (2.0%)	0.0006
Tenofovir	27 (0.9%)	18 (0.6%)	29 (0.5%)	0.1
Total therapy (d) [median (IQR)]	3 (2-5)	4 (3-6)	5 (4-8)	<0.0001

NOTE: Reported values are n (%) unless otherwise specified. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CrCl, creatinine clearance; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PTZ, piperacillin-tazobactam; SD, standard deviation; VAN, vancomycin; VAN/PTZ, vancomycin and piperacillin-tazobactam combination.

differences in AKI rates between years studied ($r^2 = 0.4732$, $P = 0.2$). Patients in the VAN/PTZ group experienced AKI on average of 8.0 days after treatment initiation, compared to 8.7 days and 5.2 days for VAN and PTZ monotherapy groups, respectively. The composite of inhospital mortality and transfer-to-hospice care was more common in VAN/PTZ patients (9.6%) compared to monotherapy groups (VAN, 3.9%; PTZ, 3.4%), most likely due to the increased severity of illness.

In the subgroup analysis of patients with similar CCI, AKI

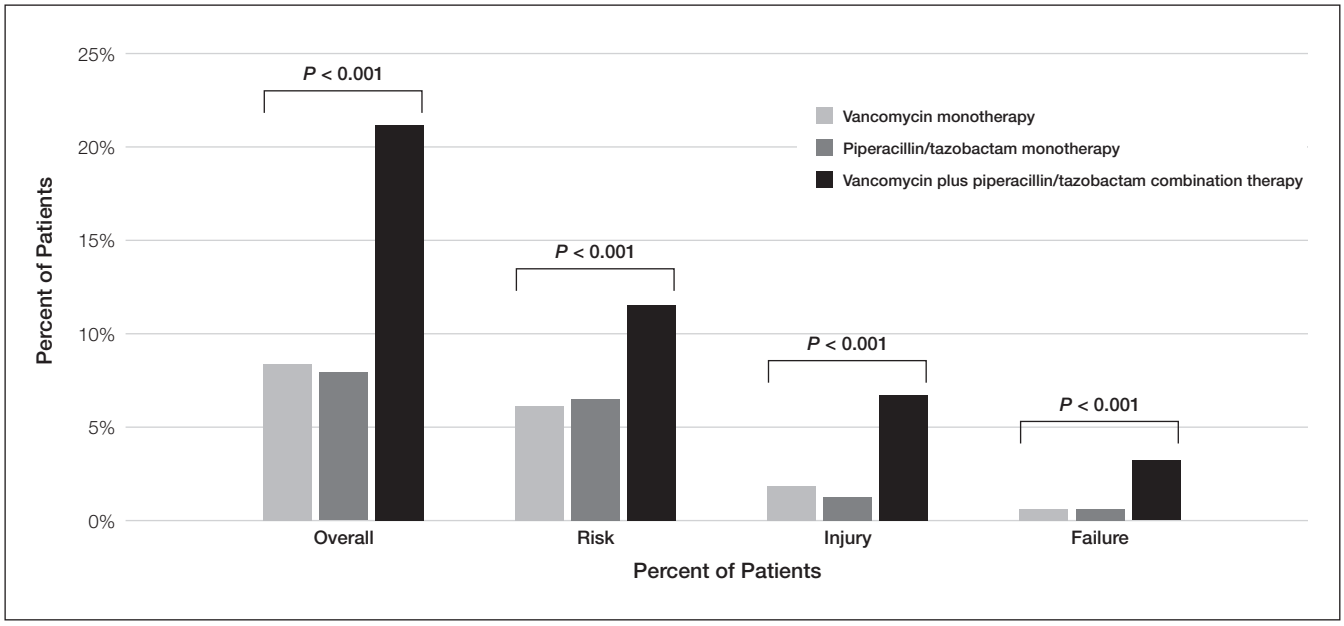

FIG. Unadjusted incidence of acute kidney injury.

incidence increased with severity of illness. When CCI was 0, 7.5% of patients experienced AKI compared to 11.2%, 16.4%, and 18.9% of patients when CCI was 1, 2 to 4, and ≥5, respectively ($P < 0.0001$). VAN/PTZ (range = 12.1% to 26.5%) was associated with greater AKI incidence than either VAN (range = 4.8% to 11.5%) or PTZ (range = 3.8% to 10.4%) alone in each subgroup ($P < 0.0001$ for all subgroups).

Factors associated with AKI in univariate analyses included treatment with VAN/PTZ, days of therapy, baseline creatinine clearance, transfer from outside hospitals, CCI, admission type, length of hospitalization, dehydration exposure, and hypotension exposure. Exposure to aminoglycosides, amphotericin B, ACE inhibitors, nonsteroidal anti-inflammatory drugs, tacrolimus, foscarnet, loop diuretics, sulfonamides, and tenofovir were all associated with increased odds of AKI in simple univariate logistic regression. Gender, age, year of treatment, angiotensin II receptor antagonist exposure, and cyclosporine exposure were not significantly associated with AKI incidence.

After multivariate logistic regression, monotherapy with VAN or PTZ was associated with decreased odds of AKI compared to VAN/PTZ therapy (aOR_{VAN}, 0.48; 95% CI_{VAN}, 0.41-0.57; aOR_{PTZ}, 0.43; 95% CI_{PTZ}, 0.37-0.50). No difference in AKI incidence was observed between VAN and PTZ groups ($aOR_{PTZ:VAN}$, 0.88; 95% CI, 0.73-1.08). Table 2 describes the relationship between AKI and other covariates included in the model. Increased odds of AKI were seen with concomitant administration of ACE inhibitors, amphotericin B, tacrolimus, loop diuretics, and tenofovir. Radio-contrast dye administration was associated with lower odds of AKI. Patients admitted urgently and emergently were at higher risk of AKI, while those admitted via the trauma center were less likely to experience AKI compared to patients who were electively admitted. Increased length of stay and duration of therapy were both associated with increased likelihood of AKI, independent of treatment group; however, durations of therapy beyond 12 days was not associated with increased AKI. Hypotension, as defined, and diagnosed dehydration both independently increased AKI odds. Aside from those older than 80 years of age, increasing age was not associated with increased AKI risk. Male gender was associated with a slight decrease in AKI rate. No evidence of overfitting was observed with the standardized Hosmer-Lemeshow *P*-value of 0.683, and the model provides good predictive accuracy with a C-statistic of 0.788.

CONCLUSIONS

Acute kidney injury secondary to VAN therapy is a well-characterized adverse effect, while AKI incidence secondary to PTZ is less understood. Additionally, there appears to be an additive effect when these agents are used in combination. This is the largest review of AKI in patients receiving VAN,PTZ, or the combination of both agents.

There is increasing evidence suggesting greater nephrotoxicity in patients treated with the combination of VAN and antipseudomonal beta-lactams. The mechanism for the apparent increase in nephrotoxicity with this drug combination is not well understood and needs further study in both animal models and humans.

Acute kidney injury rates related to VAN vary widely, with recent studies in critically ill and internal medicine patients estimated at 21% and 13.6%, respectively.[2,3] In our VAN monotherapy cohort, the AKI rate was 8.3%, with 2.3% of patients experiencing a greater than 50% decrease in creatinine clearance. Piperacillin-tazobactam-related AKI rates are not well characterized; however, a small retrospective analysis estimated that 11.1% of PTZ patients experienced acute renal failure (defined as either increase

TABLE 2. Univariate and Multivariate Association between Combination VAN/PTZ Therapy and AKI Odds Independent of Other Baseline Covariates

Covariate	Unadjusted			Adjusted		
	OR	95% CI	*P*	aOR	95% CI	*P*
Treatment group						
PTZ/VAN		(referent)			(referent)	
VAN	0.34	0.29-0.39	**<0.001**	0.48	0.41-0.57	**<0.0001**
PTZ	0.32	0.27-0.37	**<0.001**	0.43	0.37-0.5	**<0.0001**
Male gender	0.99	0.89-1.10	0.896	0.85	0.75-0.95	**0.0049**
Age (y)						
18-29		(referent)			(referent)	
30-49	1.09	0.91-1.32	0.361	0.99	0.8-1.22	0.908
50-64	1.23	1.02-1.48	**0.031**	1.06	0.85-1.31	0.618
64-79	1.11	0.91-1.36	0.316	1.17	0.92-1.5	0.209
≥80	1.12	0.84-1.47	0.427	1.77	1.26-2.48	**0.0009**
CCI (per point)	1.07	1.06-1.09	**<0.001**	1.04	1.02-1.06	**<0.0001**
Baseline CrCl (mL/min)						
30 to <60		(referent)			(referent)	
60 to <90	1.02	0.85-1.23	0.816	1.41	1.15-1.74	**0.0012**
≥90	1.7	1.45-2.01	**<0.001**	3.39	2.76-4.16	**<0.0001**
Admission type						
Elective		(referent)			(referent)	
Emergency	1.19	1.02-1.39	**0.033**	1.22	1.02-1.45	**0.033**
Trauma	1.03	0.79-1.33	0.82	0.5	0.37-0.66	**<0.0001**
Urgent	1.63	1.38-1.94	**<0.001**	1.39	1.13-1.7	**0.0016**
Transfer from outside facility	1.56	1.39-1.74	**<0.001**	1.16	1-1.33	**0.044**
Hypotension exposure	2.81	2.52-3.15	**<0.001**	1.6	1.4-1.83	**<0.0001**
Dehydration exposure	1.29	1.04-1.59	**0.018**	1.31	1.04-1.66	**0.0246**
Nephrotoxic drug exposures						
Acyclovir	1.22	0.90-1.63	0.182	1.05	0.76-1.47	0.757
ACE inhibitor	1.34	1.18-1.51	**<0.001**	1.15	1-1.33	**0.048**
Aminoglycoside	1.89	1.62-2.20	**<0.001**	1.15	0.96-1.37	0.131
Amphotericin B	4.35	2.99-6.27	**<0.001**	2.25	1.48-3.44	**0.0002**
ARB	0.87	0.65-1.15	0.347	1.17	0.85-1.59	0.335
Contrast dye	1.26	1.04-1.51	**0.017**	0.79	0.64-0.98	**0.0291**
Cyclosporine	1.35	0.50-3.06	0.506	0.74	0.26-2.12	0.571
Foscarnet	6.09	1.69-21.92	**0.004**	2.06	0.44-9.67	0.358
Loop diuretic	3.51	3.15-3.91	**<0.001**	2.02	1.77-2.31	**<0.0001**
NSAIDs	0.82	0.71-0.95	**0.009**	0.98	0.83-1.16	0.809
Sulfonamide	1.8	1.18-2.68	**0.005**	1.39	0.88-2.19	0.156
Tacrolimus	2.66	1.97-3.56	**<0.001**	2.11	1.48-3	**<0.0001**
Tenofovir	1.96	1.12-3.28	**0.013**	1.93	1.06-3.5	**0.0314**
Year of admission						
2010		(referent)				
2011	0.85	0.69-1.05	0.127			
2012	0.95	0.78-1.18	0.657			
2013	0.87	0.70-1.07	0.176			
2014	0.84	0.67-1.05	0.121			
Duration of therapy (d)						
2-3		(referent)			(referent)	
4-5	1.81	1.55-2.13	**<0.001**	1.32	1.11-1.56	**0.0013**
6-7	3.23	2.74-3.81	**<0.001**	1.8	1.5-2.15	**<0.0001**
8-9	5.09	4.22-6.13	**<0.001**	2.02	1.63-2.51	**<0.0001**
10-11	5.94	4.71-7.46	**<0.001**	1.98	1.52-2.58	**<0.0001**
12-13	5.25	3.84-7.12	**<0.001**	1.41	0.99-1.99	0.0543
≥14	5.31	4.19-6.72	**<0.001**	1.28	0.95-1.71	0.103
Length of stay (d)						
<7		(referent)			(referent)	
8-14	3.35	2.94-3.81	**<0.001**	2.05	1.76-2.39	**<0.0001**
15-21	4.48	3.79-5.29	**<0.001**	2.33	1.89-2.87	**<0.0001**
>21	5.88	5.01-6.91	**<0.001**	2.81	2.25-3.51	**<0.0001**

NOTE: Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CrCl, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; PTZ, piperacillin-tazobactam; VAN, vancomycin; VAN/PTZ, vancomycin plus piperacillin-tazobactam.

in serum creatinine greater than 0.5 mg/dL or 50% increase from baseline).[13] In the present study, we found the PTZ-related AKI rate to be 7.8%, which may be due to a more stringent definition of AKI. Additionally, Hellwig et al[13] found that PTZ monotherapy was associated with higher AKI rates compared to VAN monotherapy (11.1% vs 4.9%; $P = 0.014$). This was not replicated in our study, with VAN and PTZ monotherapy having similar AKI rates (8.3% and 7.8%, respectively) and an adjusted aOR of 0.88 (95% CI 0.0.73-1.08) for AKI in PTZ- compared to VAN-treated patients. The estimated AKI incidence of 21% in the combination therapy group at our institution is consistent with literature that ranges from 16.3% to 34.8%.[4-8, 13]

To control for differences in baseline severity of illness, we performed a subgroup analysis of patients with similar CCI scores. The finding of increased AKI in patients receiving combination VAN and PTZ was consistent in each subgroup, suggesting that the increase in AKI is independent of illness severity.

This study is not without limitations. As with all retrospective studies, it is difficult to determine a causal link between VAN and PTZ combination therapy and increased AKI incidence due to confounding. We employed a rigorous study design that controlled for major confounders of AKI, such as concomitant nephrotoxic exposure, hypotension, and renal disease. Severity of illness was measured with CCI, which may not accurately capture the severity of illness at treatment initiation. Alternatives, such as acute physiology and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA) scores, may more accurately reflect critical illness on presentation; however, this study was not focused specifically on critically ill patients. In addition to baseline comorbidity, we controlled for hypotension and dehydration as a surrogate marker for critical illness. In the subgroup analysis of patients with similar CCI, the effect of VAN/PTZ on AKI compared to VAN or PTZ monotherapy was consistent in each group. Nephrotoxic potential of agents was assumed to be equal, which is not necessarily true. Additionally, the binary representation of nephrotoxic exposure does not describe the amount of the agent received; as such, our estimations of AKI odds may be artificially elevated. Approximately one-quarter of the patients in this study were transferred from an outside hospital, for which no data regarding initial treatment are available. This may lead to exposure misclassification. We attempted to control for this factor in the regression model and found that, after controlling for other covariates, hospital transfer was associated with increasing odds of AKI. Finally, data were collected retrospectively from the electronic medical record and are subject to inaccuracies documented in the chart; however, any bias introduced should be nondifferential.

In our large retrospective study of combination empiric therapy with VAN and PTZ, we found that combination therapy was associated with more than double the odds of AKI occurring compared to either monotherapy with VAN or PTZ. Increasing duration of therapy was also associated with increases in AKI. These findings demonstrate the need for judicious use of combination therapy and strengthen the need for antimicrobial de-escalation when appropriate to avoid deleterious effects.

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The Association of Geriatric Syndromes with Hospital Outcomes

Roman Romero-Ortuno, PhD[1,3*], Duncan R. Forsyth, MA[1], Kathryn Jane Wilson, MBBS[1], Ewen Cameron, MD[2], Stephen Wallis, MB BChir[1], Richard Biram, MBBS[1], Victoria Keevil, PhD[1,3]

[1]Department of Medicine for the Elderly, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [2]Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [3]Clinical Gerontology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom

BACKGROUND: Frailty, history of dementia (HoD), and acute confusional states (ACS) are common in older patients admitted to hospital.

OBJECTIVE: To study the association of frailty (≥6 points in the Clinical Frailty Scale [CFS]), HoD, and ACS with hospital outcomes, controlling for age, gender, acute illness severity (measured by a Modified Early Warning Score in the emergency department), comorbidity (Charlson Comorbidity Index), and discharging specialty (general medicine, geriatric medicine, surgery).

DESIGN: Retrospective observational study.

SETTING: Large university hospital in England.

PATIENTS: We analyzed 8202 first nonelective inpatient episodes of people aged 75 years and older between October 2014 and October 2015.

MEASUREMENTS: The outcomes studied were prolonged length of stay (LOS ≥10 days), inpatient mortality, delayed discharge, institutionalization, and 30-day readmission. Statistical analyses were based on multivariate regression models.

RESULTS: Independently of controlling variables, prolonged LOS was predicted by CFS ≥6: odds ratio (OR) =1.55; 95% confidence interval [CI], 1.36-1.77; $P < 0.001$; HoD: OR = 2.16; 95% CI, 1.79-2.61; $P < 0.001$; and ACS: OR = 3.31; 95% CI, 2.64-4.15; $P < 0.001$. Inpatient mortality was predicted by CFS ≥6: OR = 2.29; 95% CI, 1.79-2.94; $P < 0.001$. Delayed discharge was predicted by CFS ≥6: OR = 1.46; 95% CI, 1.27-1.67; $P < 0.001$; HoD: OR = 2.17; 95% CI, 1.80-2.62; $P < 0.001$; and ACS: OR = 2.29; 95% CI: 1.83-2.85; $P < 0.001$. Institutionalization was predicted by CFS ≥6: OR = 2.56; 95% CI, 2.09-3.14; $P < 0.001$; HoD: OR = 2.51; 95% CI, 2.00-3.14; $P < 0.001$; and ACS: OR 1.93; 95% CI, 1.46-2.56; $P < 0.001$. Readmission was predicted by ACS: OR = 1.36; 95% CI, 1.09-1.71; $P = 0.006$.

CONCLUSIONS: Routine screening for frailty, HoD, and ACS in hospitals may aid the development of acute care pathways for older adults. *Journal of Hospital Medicine* 2017;12:83-89.

Geriatric syndromes are multifactorial health conditions that affect older people and include dementia, delirium, impaired mobility, falls, frailty, poor nutrition, weight loss, incontinence, and difficulties with activities of daily living.[1] These syndromes are highly prevalent among older patients admitted to acute-care hospitals[2,3] and often add complexity to the clinical status of hospitalized older adults with multiple comorbid conditions.[4] In the English National Health Service (NHS), the proportion of older people admitted to acute-care hospitals with geriatric syndromes has increased dramatically.[5]

The recognition and management of geriatric syndromes by hospitalists requires specific knowledge and skill sets.[6] However, geriatricians are a scarce resource in many settings, including the NHS. A challenge for service evaluation and research is the generally poor capture of information about geriatric syndromes compared to specific comorbidities in discharge summaries and hospital coding.[7] Steps are being taken in the NHS to address this issue, and in 2013 our center started the routine collection of data on clinical frailty, history of dementia (HoD) and acute confusional state (ACS) in all patients 75 years or older admitted nonelectively to the hospital.[8]

The presence of geriatric syndromes in older inpatients is an important driver of adverse outcomes, particularly length of stay (LOS) and admission to institutional care.[9] However, acute illness severity (AIS) is also an important determinant of poor outcomes in the inpatient population and may drive disproportionate changes in health status in the most vulnerable.[10] Research studies with geriatric syndromes in acute settings have not been able to simultaneously consider AIS.[11] In addition, comorbidity is not always associated with an increased number of geriatric syndromes.[12]

We aimed to study the association of geriatric syndromes such as frailty, HoD and ACS that are measured in routine clinical care with hospital outcomes (prolonged LOS, inpatient mortality, delayed discharge, institutionalization, and 30-day readmission), while controlling for demographics (age, gender), AIS, comorbidity, and discharging specialty (general medicine, geriatric medicine, surgery).

PATIENTS AND METHODS

Study Design and Setting

This retrospective observational study was conducted in a large tertiary university hospital in England with 1000 acute beds receiving more than 102,000 visits to the emergency

***Address for correspondence and reprint requests**: Roman Romero-Ortuno, PhD, Department of Medicine for the Elderly, Box 135, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom; Telephone: +441223217786; Fax: +441223217783; E-mail: roman.romero-ortuno@nhs.net

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TABLE 1. ED-MEWS: Components and Scoring

	Score						
Component	3	2	1	0	1	2	3
HR	<40	41-50	51-60	61-90	91-110	111-129	≥130
RR	≤6	7-8	-	9-14	15-20	21-29	≥30
SBP	≤70	71-80	81-100	101-180	-	≥181	-
AVPU	U	P	V	A			
GCS				15	14	9-13	≤8
Temp	-	<35.0	-	35.0-38.4	-	38.5-39.0	≥39.0

NOTE: ED-MEWS, Emergency Department Modified Early Warning Score; minimum score = 0 points, maximum score = 15 points. Abbreviations: AVPU, alert, responds to voice, responds to pain, unresponsive; GCS, Glasgow Coma Scale; HR, heart rate (beats per minute); RR: respiratory rate (per minute); SBP: systolic blood pressure (mm Hg); temp, body temperature (degrees Celsius).

department (ED) and admitting over 73,000 patients per year; among the latter, more than 12,000 are 75 years and older.

Sample

We analyzed all first nonelective inpatient episodes (ie, from ED admission to discharge) of people 75 years and older (all specialties) between the October 26, 2014 and the October 26, 2015. Data were obtained via the hospital's information systems following the implementation of a new electronic patient record on October 26, 2014.

Patients' Characteristics

The following anonymized variables were extracted:

- Age and gender
- AIS information is routinely collected in our ED using a Modified Early Warning Score (ED-MEWS). The components and scoring of ED-MEWS are shown in Table 1. Where more than 1 ED-MEWS was collected, the highest was used in the analyses.
- Charlson Comorbidity Index (CCI, without age adjustment).[13] The CCI is based on the discharge diagnoses, as coded according to WHO International Classification of Diseases, v 10 (ICD-10). The CCI was calculated retrospectively and would have not been available to clinicians early during the patients' admission.
- Clinical Frailty Scale (CFS). The scoring of CFS is based on a global assessment of patients' comorbidity symptoms, and their level of physical activity and dependency on activities of daily living, estimated to reflect the status immediately before the onset of the acute illness leading to hospitalization. The possible scores are: 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill) (http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm).[14] The use of the CFS in admissions of people 75 years and older was introduced in our center in 2013 under a local Commissioning for Quality and Innovation (CQUIN) scheme.[8] The CQUIN required that all patients 75 years and older admitted to the hospital, via the ED, be screened for frailty using the CFS within 72 hours of admission. The admitting doctor usually scores the CFS on the electronic admission record, but it can also be completed by ED nurses or by nursing or therapy staff from the trust-wide Specialist Advice for the Frail Elderly team. Training on CFS scoring is provided to staff at a hiring orientation and at regular educational meetings. Permission to use CFS for clinical purposes was obtained from the principal investigator at Geriatric Medicine Research, Dalhousie University, Halifax, Canada.
- Cognitive variables were collected early during the admission in patients 75 years and older, thanks to a parallel local CQUIN scheme. The cognitive CQUIN variables are screening variables, not gold standard. The admission clerking is designed to clinically classify patients within 72 hours of admission into the following 3 mutually exclusive categories:
  - Known HoD (in the database: no = 0; yes = 1)
  - ACS, without HoD (in the database: no = 0; yes = 1)
  - Neither HoD nor ACS
- The cognitive CQUIN assessment does not intend to diagnose dementia in those who are not known to have it, but tries to separate the dementias that general practitioners (GPs) know from hospital-identified acute cognitive concerns that GPs may need to assess or investigate after discharge. The latter may include delirium and/or undiagnosed dementia.
- In our routine hospital practice, the initial cognitive assessment is performed by a clinician in the following fashion: if the patient is known to have dementia (ie, based on clinical history and/or chart review), the clinician selects the "known history of dementia" option in the admission navigator, and no further cognitive screening is conducted. If the patient has no known dementia, the clinician administers the 4-item Abbreviated Mental Test (AMT4): (1) age, (2) date of birth, (3) place, and (4) year, with impaired cognition indicated by an AMT4 of less than 4 and triggering the selection of "ACS without known HoD" option. If the AMT4 is normal, the clinician selects the "neither HoD nor ACS" option.
- Due to the service evaluation nature of our work, these measures could not be assessed for reliability within the electronic medical records system (eg, regarding sensitiv-

ity and specificity against a gold standard or inter-rater reliability).

- Discharged from geriatric medicine (no = 0; yes = 1). Every year, our hospital admits over 12,000 patients 75 years and older, of which 25% are managed by the Department of Medicine for the Elderly (DME). The DME specialist bed base consists of 5 core wards, which specialize in ward-based comprehensive geriatric assessment (CGA) and are supported by dedicated nursing, physiotherapy, occupational therapy, and social work teams, as well as by readily available input from speech and language therapy, clinical nutrition, psychogeriatric, pharmacy and palliative care teams. Formal multidisciplinary team meetings occur at least twice weekly. A sixth specialist DME ward with a more acute perspective has been operational for 7 years; this ward was renamed the Frailty and Acute Medicine for the Elderly (FAME) ward in 2014 and has daily multidisciplinary team meetings. Although admission to FAME is through the ED, admission to core DME wards can occur from FAME (ie, within-DME transfer), via the ED, or from other inpatient specialty areas if older patients are perceived to be in high need of CGA after screening by the Specialist Advice for the Frail Elderly team. An audit in our center showed that up to 20% of patients discharged by DME were not initially admitted by DME, underscoring the significant role of core specialist DME wards in absorbing complex cases, especially from the general medical wards.[8]
- Discharged from general medicine (no = 0; yes = 1). In our setting, virtually all patients discharged by general medicine were first admitted by general medicine.[8]
- Discharged by a surgical specialty (no = 0; yes = 1)

Hospital Outcomes

The following anonymized variables were identified:

- LOS) (days). Prolonged LOS was defined as 10 or more days (no = 0; yes = 1)
- Inpatient mortality (no = 0; yes = 1)
- Delayed discharge (no = 0; yes = 1). This was defined as the total LOS being at least 1 day longer than the LOS up to the last recorded clinically fit date. This date is used in NHS hospitals to indicate that the acute medical episode has finished and discharge-planning arrangements (often via social care providers) can commence.
- Institutionalization (no = 0; yes = 1). This was defined as the discharge destination being a care home, when a care home was not the usual place of residence.
- 30-day readmission (no = 0; yes = 1)

Statistical Analyses

Anonymized data were analyzed with IBM SPSS Statistics (v 22, Armonk, New York) software. Descriptive statistics were given as count (with percentage) or mean (with standard deviation.

To avoid potential problems with multicollinearity in the multivariate regression models, the correlations among the predictor variables were checked using a correlation matrix of 2-sided Spearman's *rho* correlation coefficients. Correlations of 0.50 or more were considered large.[15,16]

Because all outcomes in the study were binary, multivariate binary logistic regression models were computed. In these models, the odds ratio (OR) reflects the effect size of each predictor; 95% confidence intervals (CI) were requested for each OR. Predictors with $P < 0.01$ were considered as statistically significant. The classification performance of each logistic regression model was assessed calculating its area under the curve (AUC).

Sensitivity analyses were conducted after imputing missing data (SPSS multiple imputation procedure) and after fitting interaction terms between geriatric syndromes and discharge by geriatric medicine.

RESULTS

The initial database contained 12,282 nonelective admission and discharge episodes (all specialties) of patients 75 years and older between October 26, 2014 and October 26, 2015. Among those, 8202 (66.8%) were first episodes. Table 2 shows the sample descriptives, and Table 3 shows the breakdown of geriatric syndromes (single and multiple) in the total sample (n = 8282), including missing frailty data.

In the correlation matrix of 2-sided Spearman's *rho* correlation coefficients, no correlations with large-effect size were found to suggest issues with multicollinearity; the largest correlation coefficients were between age and CFS (*rho* = 0.35), HoD and CFS (*rho* = 0.32), and CCI and CFS (*rho* = 0.26).

The results of the multivariate regression models are shown in Table 4. The best performing models were the ones for inpatient mortality (AUC = 0.80), followed by institutionalization (AUC = 0.76), and prolonged LOS (AUC = 0.71). After full adjustment, clinical frailty was an independent predictor of prolonged LOS, inpatient mortality, delayed discharge, and institutionalization. HoD was an independent predictor of prolonged LOS, delayed discharge, and institutionalization; and ACS was an independent predictor of prolonged LOS, delayed discharge, institutionalization, and 30-day readmission (Table 4). Results did not significantly change in sensitivity analyses conducted after multiple imputation of missing data and after inclusion of interaction terms (see Supplemental Table 1 and Supplemental Table 2).

DISCUSSION

Our aim was to study the association of geriatric syndromes (measured in routine clinical care) with hospital outcomes. We found that geriatric syndromes such as clinical frailty, HoD, and ACS were strong independent predictors. Concerning prolonged LOS, delayed discharge, and institutionalization, geriatric syndromes had ORs that were greater than those of traditionally measured factors such as demographics, comorbidity and acute illness severity. Our findings add to the body of knowledge in this area because we

TABLE 2. Sample Descriptives (8202 First Admission and Discharge Episodes)

	% (n) or mean (range; SD)
Age, y	84.1 (75 to 105; 5.9)
Female gender	56.5% (4631)
ED-MEWS	2.9 (0 to 12; 1.8)
CCI	2.9 (0 to 23; 3.1)
CFS	4.8 (1 to 9; 1.7)
CFS 1: very fit	1.1% (92)
CFS 2: fit	4.6% (381)
CFS 3: managing well	14.1% (1159)
CFS 4: vulnerable	11.8% (968)
CFS 5: mildly frail	12.4% (1021)
CFS 6: moderately frail	16.1% (1324)
CFS 7: severely frail	9.0% (736)
CFS 8: very severely frail	2.1% (169)
CFS 9: terminally ill	0.6% (49)
CFS missing	28.1% (2303)
HoD	9.9% (812)
ACS	6.3% (519)
Discharge from general medicine	33.1% (2715)
Discharge from geriatric medicine	22.2% (1817)
Discharge from surgery	27.9% (2289)
LOS, d	8.9 (0 to 209; 12.7)
LOS ≥10 d	30.3% (2488)
Inpatient mortality	7.4% (604)
Delayed discharge	26.3% (2158)
Institutionalization	9.9% (809)
30-d readmission	29.8% (2447)

NOTE: Abbreviations: ACS, acute confusional state; CFS, Clinical Frailty Scale; CCI, Charlson Comorbidity Index; ED-MEWS, Emergency Department Modified Early Warning Score; HoD, history of dementia; LOS, length of stay; n, number; SD, standard deviation.

TABLE 3. Geriatric Syndromes (Single and Multiple) in Total Sample, Including Missing Frailty Data[a]

						Count
CFS ≥6	No (3621)	HoD	No (3493)	ACS	No	3332
					Yes	161
			Yes (128)	ACS	No	128
					Yes	0
	Yes (2278)	HoD	No (1742)	ACS	No	1490
					Yes	252
			Yes (536)	ACS	No	536
					Yes	0
	Missing (2303)	HoD	No (2155)	ACS	No	2049
					Yes	106
			Yes (148)	ACS	No	148
					Yes	0

[a]n = 8282.

NOTE: Abbreviations: ACS, acute confusional state; CFS, Clinical Frailty Scale; HoD, history of dementia.

accounted for the latter effects. Our experience shows that metrics on geriatric syndromes can be successfully collected in the routine hospital setting and add clear value to the prediction of operational outcomes. This may encourage other hospitals to do the same.

Our findings are consistent with suggestions that accounting for chronic conditions alone may be less informative than also accounting for the co-occurrence of geriatric syndromes.[17] The focus of CFS is on the pre-admission level of physical activity and dependency on activities of daily living, and poorer scores may confer vulnerability to adverse outcomes due to reduced physiological reserve and ability to withstand acute stressors.[18] Other studies have also found CFS to be a good predictor of inpatient outcomes,[19-22] and it has been recommended as a possible means to identify vulnerable older adults in acute-care settings.[23]

HoD and ACS had independent effects beyond frailty, particularly in prolonging LOS, delaying discharge, and requiring institutionalization. Dementia prolongs LOS,[24] and delirium prolongs hospitalization for persons with dementia.[25] Older people with cognitive impairment may have an increased risk of acquiring new geriatric syndromes during hospitalization, particularly if it is prolonged.[26] One study showed that the risk of poor functional recovery can be as high as 70% in complex delirious patients in hospital.[27] All too often, delirium is neither benign nor reversible, with a significant proportion of patients not experiencing restoration *ad integrum* of cognition and function.[28]

Our results are consistent with observations that geriatric syndromes are associated with higher risk of institutionalization.[29] It was interesting that female gender seemed to be an independent predictor of institutionalization, which is consistent with the results of a systematic review showing that the male-to-female ratio of admission rates ranged between 1 to 1.4 and 1 to 1.6.[30]

Discharge by general medicine appeared to be associated with a lower likelihood of prolonged LOS, and discharge by geriatric medicine seemed to be associated with a higher likelihood of delayed discharge and institutionalization. Unsurprisingly, geriatric medicine wards tend to absorb the most complex cases, often with complex discharge planning needs.[8] In that light, CGA in geriatric wards may not be associated with reduced LOS (and it is possible that the LOS of complex patients might have been higher in nongeriatric wards). In addition, inpatient CGA increases frail patients' likelihood of survival.[31]

Our study suggests that routinely collected metrics on frailty, HoD and ACS may be helpful to better adapt hospital care to the real requirements of aged people. The proportion of older people admitted to acute hospitals with geriatric syndromes continues to increase[5] and geriatricians are a scarce resource. It will be increasingly important to upskill nongeriatric hospitalists in the recognition and management of geriatric syndromes. Frail older people are becom-

TABLE 4. Results of Multivariate Regression Models

Dependent variable: LOS ≥10 d (n = 5546); chi-square = 708.1; *P* < 0.001; AUC = 0.71)						
	Unstandardized coefficients			95% CI for OR		
	B	Std. error	OR	Lower bound	Upper bound	*P*
Age	0.01	0.01	1.01	1.00	1.03	0.009
Gender	0.07	0.06	1.08	0.95	1.22	0.234
ED-MEWS	0.11	0.02	1.12	1.08	1.16	<0.001
CCI	0.09	0.01	1.09	1.07	1.11	<0.001
CFS ≥6	0.44	0.07	1.55	1.36	1.77	<0.001
HoD	0.77	0.10	2.16	1.79	2.61	<0.001
ACS	1.20	0.12	3.31	2.64	4.15	<0.001
Dc gen med	-0.87	0.09	0.42	0.35	0.51	<0.001
Dc geri med	0.00	0.10	1.00	0.83	1.21	0.995
Dc surgery	0.08	0.10	1.09	0.89	1.32	0.411
Dependent variable: inpatient mortality (n = 5546; chi-square = 447.7; *P* < 0.001; AUC = 0.80)						
	B	Std. error	OR	95% CI for OR		*P*
Age	0.05	0.01	1.05	1.03	1.07	<0.001
Gender	-0.17	0.12	0.85	0.67	1.06	0.145
ED-MEWS	0.40	0.03	1.49	1.41	1.57	<0.001
CCI	0.15	0.02	1.17	1.13	1.20	<0.001
CFS ≥6	0.83	0.13	2.29	1.79	2.94	<0.001
HoD	-0.37	0.16	0.69	0.50	0.95	0.024
ACS	0.17	0.19	1.19	0.82	1.72	0.363
Dc gen med	0.22	0.18	1.24	0.88	1.75	0.222
Dc geri med	0.06	0.19	1.06	0.74	1.52	0.759
Dc surgery	0.07	0.22	1.07	0.70	1.65	0.746
Dependent variable: Delayed discharge (n = 4984; chi-square = 416.6; *P* < 0.001; AUC = 0.68)						
	B	Std. error	OR	95% CI for OR		*P*
Age	0.03	0.01	1.03	1.02	1.05	<0.001
Gender	0.00	0.07	1.00	0.88	1.13	0.953
ED-MEWS	-0.03	0.02	0.98	0.94	1.01	0.182
CCI	0.03	0.01	1.03	1.00	1.05	0.018
CFS ≥6	0.38	0.07	1.46	1.27	1.67	<0.001
HoD	0.78	0.10	2.17	1.80	2.62	<0.001
ACS	0.83	0.11	2.29	1.83	2.85	<0.001
Dc gen med	-0.23	0.10	0.80	0.66	0.97	0.021
Dc geri med	0.36	0.10	1.44	1.18	1.75	<0.001
Dc surgery	-0.10	0.11	0.90	0.73	1.12	0.358

Continued on page 88

ing the core business of acute hospitals,[32] making geriatrics "too important to be left to geriatricians."[33] Therefore, easily collected metrics on geriatric syndromes may help nongeriatricians identify these syndromes and address them early during admission.

Our study has important limitations. Firstly, geriatric syndromes were not identified with gold-standard measures. For example, ACS in the absence of known dementia should be seen only as a surrogate for delirium. ACS as a proxy measure is likely to underestimate the diagnosis of delirium, be-

TABLE 4. Results of Multivariate Regression Models *(continued)*

Dependent variable: Discharge to Care Home (Institutionalization) (n = 5546; Chi-square = 473.5; $P < 0.001$; AUC = 0.76)						
	B	Std. error	OR	95% CI for OR		*P*
Age	0.03	0.01	1.03	1.02	1.05	<0.001
Gender	0.34	0.10	1.40	1.16	1.69	<0.001
ED-MEWS	0.03	0.03	1.03	0.98	1.08	0.266
CCI	0.03	0.02	1.03	1.00	1.06	0.055
CFS ≥6	0.94	0.10	2.56	2.09	3.14	<0.001
HoD	0.92	0.11	2.51	2.00	3.14	<0.001
ACS	0.66	0.14	1.93	1.46	2.56	<0.001
Dc gen med	-0.02	0.16	0.98	0.71	1.34	0.884
Dc geri med	0.64	0.16	1.90	1.40	2.58	<0.001
Dc surgery	0.11	0.18	1.12	0.79	1.60	0.535
Dependent variable: 30-d readmission (n = 5546; Chi-square = 103.0; $P < 0.001$; AUC = 0.59)						
	B	Std. error	OR	95% CI for OR		*P*
Age	0.02	0.01	1.02	1.01	1.03	0.001
Gender	-0.05	0.06	0.95	0.85	1.07	0.412
ED-MEWS	-0.06	0.02	0.94	0.91	0.98	0.001
CCI	0.05	0.01	1.06	1.04	1.08	<0.001
CFS ≥6	0.09	0.07	1.10	0.96	1.25	0.171
HoD	0.10	0.10	1.10	0.91	1.34	0.309
ACS	0.31	0.11	1.36	1.09	1.71	0.006
Dc gen med	0.19	0.09	1.21	1.01	1.44	0.041
Dc geri med	-0.03	0.10	0.97	0.80	1.17	0.737
Dc surgery	-0.22	0.11	0.80	0.66	0.99	0.037

NOTE: The reference category for gender is male (male = 0; female = 1). Abbreviations: ACS, acute confusional state; AUC, area under the curve; CFS, Clinical Frailty Scale; CCI, Charlson Comorbidity Index; CI, confidence interval; Dc, discharge; ED-MEWS, Emergency Department Modified Early Warning Score; Gen Med, General Medicine; Geri Med, Geriatric Medicine; HoD, history of dementia; LOS, length of stay; n, number; OR, odds ratio.

cause the hypoactive type is commonly missed without valid measures. In addition, a patient with delirium superimposed upon dementia would have been coded as a 'known dementia.' The geriatric syndromes' measures could not be assessed for reliability within the electronic medical records system (eg, regarding sensitivity and specificity against a gold standard, or interrater reliability).

About the potential limitations of CFS, there have been concerns that an interobserver discrepancy in CFS scoring may occur between health professionals. However, 1 study investigated the interrater reliability of CFS between clinicians in 107 community-dwelling older adults 75 years and older, finding a substantial agreement with a weighted κ coefficient of 0.76 (95% CI: 0.68 to 0.85).[34] Another study reported a CFS-weighted kappa of 0.92.[35] Another limitation of CFS in our center is the significant proportion of missing data (28%). As we have shown, missing CFS data are more frequent in situations of very high acuity (including in critical care or surgical areas) or in medical areas when the LOS was short (eg, less than 72 hours).[8] We tried to address this bias by performing multiple imputation for missing data, which showed similar results.

Another limitation of our study is that we treated geriatric syndromes and the other predictors in the models as independent variables. However, many of the factors may be interrelated, and they present simultaneously in many patients. Indeed, the bivariate correlation between CFS and HoD was of moderate strength, because worsening cognition should score higher on CFS according to the scoring protocol. As expected, there was also a medium-sized correlation between CFS and CCI. It has been suggested that physical and cognitive frailty may be more informative as a single complex phenotype.[36] Indeed, the problems of old age tend to come as a package.[37]

For 30-day readmission, the AUC of the model was small, suggesting the existence of unmeasured explanatory variables. For example, although our results agree that AIS and chronic illness predict readmission,[38] the latter still remains an elusive outcome, and a more accurate prediction may be attained by adding socioeconomic variables to models.[39]

Our study echoes the potential utility of incorporating common geriatric clinical features in routine clinical examination and disposition planning for older patients in acute settings.[40]

Hospitals may find it informative to undertake large-scale screening for geriatric syndromes including frailty, dementia, and delirium in all older adults admitted via the ED. When combined with other routinely collected variables such as demographics, AIS, and comorbidity data, this process may provide hospitals with information that will help define the acute needs of the local population and aid in the development of care pathways for the growing population of older adults.

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Patient-Level Exclusions from mHealth in a Safety-Net Health System

Keiki Hinami, MD, MS[1*], Bhrandon A. Harris, MD[2], Ricardo Uriostegui, MD[2], Wilnise Jasmin, MD, MBA[2], Mario Lopez, MD[2], William E. Trick, MD[1]

[1]Collaborative Research Unit, Department of Medicine, Cook County Health and Hospitals System, Chicago, Illinois; [2]Department of Family Medicine, Cook County Health and Hospitals System, Chicago, Illinois

Excitement about mobile health (mHealth) for improving care transitions is fueled by widespread adoption of smartphones across all social segments, but new disparities can emerge around nonadopters of technology-based communications. We conducted a cross-sectional survey of urban low-income adults to assess inadequate reading health literacy and limited English proficiency as factors affecting access to and engagement with mHealth. Although the proportion owning smartphones were comparable to national figures, adjusted analysis showed fewer patients with inadequate reading health literacy having Internet access (odds ratio [95% confidence interval]: 0.50 [0.26-0.95]), e-mail (0.43 [0.24-0.79]), and interest in using e-mail (0.34 [0.18-0.65]) for healthcare communications. Fewer patients with limited English proficiency were interested in using mobile apps (0.2 [0.09-0.46]). Inpatient status was independently associated with less interest in text messaging (0.46 [0.25-0.87]). mHealth exclusions around literacy and language proficiency threaten equity, and innovative solutions are needed to realize mHealth's potential for reducing disparities. *Journal of Hospital Medicine* 2017;12:90-93. © 2017 Society of Hospital Medicine

Interest in mHealth—the use of mobile communication devices for clinical and public health—has exploded among clinicians and researchers for its potential to efficiently improve patient health. Recent studies have used mHealth's asynchronous receptive and expressive communication functions in interventions targeted to managing care transitions and hospital readmissions.[1-3] We also recently published on improved readmission risk assessments using post-discharge measures of patient reported outcomes, which could be collected through mobile devices.[4] But persistent disparities in access to[5] and engagement with[6] smartphones may threaten validity and equity when mHealth strategies do not fully address its own limitations.

Disparities introduced by uneven access to technology are well known, but the rapid, albeit belated, adoption of mobile devices by racial minority groups in the United States has allowed authors of recent thoughtful publications to recast mHealth as itself offering solutions to the disparities' problem.[7,8] Others have cautioned the emergence of disparities along domains other than race, such as low literacy and limited English proficiency (LEP).[9] In this paper, we assessed the impact of inadequate reading health literacy (IRHL) and LEP on factors related to access and engagement with mHealth. We conducted our study among urban low-income adults in whom IRHL and LEP are common.

***Address for correspondence and reprint requests:** Keiki Hinami, MD, MS, 1900 W. Polk St., Rm 1412, Chicago IL 60612; Telephone: 312-864-3647; Fax: 312-864-9694; E-mail: khinami@cookcountyhhs.org

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METHODS

We surveyed patients in a large public safety-net health system serving 132 municipalities, including the city of Chicago, in northeastern Illinois. In 2015, nearly 90% of patients were racial-ethnic minorities with more than one-third insured by Medicaid and another one-third uninsured. We sampled adult inpatients and outpatients separately by nonselectively approaching patients in November 2015 to complete an in-person questionnaire in a 464-bed hospital and in 2 primary-care clinics. All inpatients occupied a non-isolation room in a general medical-surgical ward that had been sampled for data collection for that day in 9-day cycles with 8 other similar units. All outpatients in the clinic waiting areas were approached on consecutive days until a predetermined recruitment target was met. Each participant was surveyed once in his/her preferred language (English or Spanish), was 18 years and older, consented verbally, and received no compensation. Sample size provided 80% power to detect a device ownership rate of 50% in an evenly allocated low literacy population compared to a reference rate of 66% assuming a 2-sided α of 0.05 using the Fisher exact test.

The 18-item questionnaire was informed by constructs addressed in the 2015 Pew Research Center smartphone survey.[10] However, in addition to device ownership, we inquired about device capabilities, service-plan details, service interruptions due to difficulty paying bills in the previous year, home-Internet access, an active e-mail account, and self-assigned demographics. Self-reported reading health literacy,[11] more directly measured than e-health literacy, was screened using a parsimonious instrument validated as a dichotomized measure.[12] Instruments in English and Spanish were tested for appropriate and comprehensible word choices and syntax through pilot testing. We inferred LEP among patients preferring to complete the survey in Spanish based

on our familiarity with the population. We defined any Internet access as having a mobile data-service plan or having home-Internet access. In addition, we inquired about primary insurance provider and offered Medicaid patients an informational brochure about the federal Lifeline Program (https://www.fcc.gov/lifeline) that subsidizes text-messaging-enabled cellular telephone service for low-income patients. Notably, we assessed engagement by asking about the extent of patients' interest in "new ways of communicating with your doctor, clinic, or pharmacy using" text, e-mail, or mobile apps with a 5-level response scale ranging from "not at all interested" to "very interested".

Participant characteristics were confirmed to be similar to the Cook County Health and Hospitals System patient population in 2015 with regards to age, gender, and race/ethnicity. We calculated unadjusted and adjusted odds ratios for IRHL and LEP's association with each dependent measure of access (to smartphone, Internet, or e-mail) and engagement (using text messaging, e-mail, or mobile apps) controlling for age, gender, primary payer, recruitment location, IRHL, and LEP. Because we oversampled inpatients, we estimated sampling-weight-adjusted proportions and 95% confidence intervals (CI) of the entire CCHHS patient population with access to smartphone, data/text plan, non-prepaid plan, and service interruptions using STATA v13 (StataCorp LP, College Station Texas). The project received a waiver upon review by the local Institutional Review Board.

RESULTS

Participation rate was 65% (302/464). Differences in patients by site are shown in Table 1. IRHL was more frequent and LEP less frequent among hospitalized patients. As shown in Table 2, patients with IRHL were less likely to have any Internet access, to have an active e-mail account, and to be interested in using e-mail for healthcare communications. Patients with LEP were less likely than English speakers to be interested in using mobile apps. Inpatients were less likely than outpatients to be interested in text messaging for healthcare communications.

The estimated proportion (95% CI) of the health system's patients owning a text-enabled mobile device was 87% (75%-94%) and an Internet-enabled mobile device was 64% (47%-78%). The proportion with no data service interruptions in the previous year was 40% (31%-50%).

TABLE 1. Characteristics of Patients Recruited from an Urban Safety-Net Healthcare System in November 2015 and Their Access to and Engagement with mHealth by Recruitment Site

	Inpatient	Outpatient
N	100	202
Age category, n (%)		
18-30	10 (10)	37 (18)
31-50	30 (30)	57 (28)
51-65	48 (48)	76 (38)
>65	12 (12)	32 (16)
Women, n (%)	37 (37)	133 (66)
Race-ethnicity category, n (%)		
Non-Hispanic black	57 (57)	102 (50)
Latino	26 (26)	97 (48)
Non-Hispanic white	11 (11)	3 (1)
Other	6 (6)	0 (0)
US citizen, n (%)	71 (71)	132 (65)
Primary payer, n (%)		
Self-pay	49 (49)	75 (37)
Medicaid or dual eligible	28 (28)	97 (48)
Medicare	8 (8)	12 (6)
Private	6 (6)	14 (7)
Other	9 (9)	4 (2)
Positive inadequate health literacy screen, n (%)	47 (47)	70 (35)
LEP Spanish speakers, n (%)	20 (20)	101 (50)
Ownership of mobile device functionality, n (%)		
Text messaging	95 (95)	179 (89)
Internet	56 (56)	128 (63)
Uninterrupted data service plan, n (%)	33 (33)	87 (43)
Active e-mail account, n (%)	49 (49)	115 (57)
Any Internet access, n (%)	74 (74)	142 (70)
Interest in text for healthcare communications, n (%)	65 (65)	95 (47)
Interest in e-mail for healthcare communications, n (%)	42 (42)	80 (40)
Interest in apps for healthcare communications, n (%)	24 (24)	54 (27)

NOTE: Abbreviation: LEP, limited English proficiency.

DISCUSSION

In this cross-section of urban low-income adult patients, IRHL and LEP were factors associated with potential disparities introduced by mHealth. Even as access to smartphones becomes ubiquitous, lagging access to Internet and e-mail among low literacy patients, and low levels of technology engagement for healthcare communications among patients with IRHL or LEP, underscore concerns about equity in health systems' adoption of mHealth strategies. Hospitalized patients were found to have diminished engagement with mHealth independent of IRHL and LEP.

Regarding engagement, significantly fewer patients with IRHL or LEP were interested in using technology for healthcare communications. Our finding suggests that health disparities already associated with these conditions[13] may not be reduced by mobile device outreach alone and may even be worsened by it. Touch screens, audio-enabled questionnaires, and language translation engines are innovations that may be helpful to mitigate IRHL and LEP, but evidence is scarce. Privacy and security concerns, and lack of experience with technology, may also lower engagement. A contemporaneous study found lower apps' usage among Latinos, also suggesting that language concordance between apps, their source, and targeted users is important.[14] Low-tech solutions involving mobile telephone or even lower tech in-person communications targeted to the estimated 26% of the US population with low literacy[15] and 20% with LEP[16] may be practical stopgap measures. Even as disparities

TABLE 2. ORs and 95% CIs for IRHL, LEP, and Inpatient Status Associated with Technology Access and Engagement Controlling for Age, Gender, and Primary Payer

	Inadequate health literacy			Limited English proficiency			Inpatient		
	Unadjusted Odds Ratio	Adjusted Odds Ratio	*P*	Unadjusted Odds Ratio	Adjusted Odds Ratio	*P*	Unadjusted Odds Ratio	Adjusted Odds Ratio	*P*
Access to a smartphone	0.26 (0.11-0.61)	0.40 (0.16-1.03)	0.06	0.40 (0.18-0.88)	0.55 (0.18-1.69)	0.30	0.41 (0.15-1.11)	0.35 (0.11-1.13)	0.08
Any internet access	0.30 (0.18-0.51)	0.50 (0.26-0.95)	0.03	0.60 (0.36-1.00)	1.04 (0.48-2.25)	0.93	0.83 (0.48-1.43)	0.74 (0.36-1.53)	0.41
Active email account	0.26 (0.16-0.42)	0.43 (0.24-0.79)	<0.01	0.62 (0.39-0.98)	0.89 (0.45-1.79)	0.75	1.38 (0.85-2.23)	1.38 (0.71-2.66)	0.34
Interested in using text messaging	0.72 (0.45-1.14)	1.29 (0.70-2.37)	0.41	0.48 (0.30-0.77)	0.62 (0.33-1.18)	0.15	0.48 (0.29-0.78)	0.46 (0.25-0.87)	0.02
Interested in using email	0.25 (0.15-0.42)	0.34 (0.18-0.65)	<0.01	0.60 (0.37-0.96)	0.99 (0.51-1.91)	0.98	0.91 (0.56-1.47)	0.74 (0.39-1.41)	0.36
Interested in using mobile apps	0.53 (0.30-0.93)	1.36 (0.68-2.75)	0.38	0.29 (0.16-0.54)	0.20 (0.09-0.46)	<0.01	1.16 (0.66-2.01)	0.74 (0.47-1.49)	0.40

NOTE: Abbreviations: CI, confidence interval; IRHL, inadequate reading health literacy; LEP, limited English proficiency; OR, odds ratio.

in access to technology across race-ethnicity are diminishing,[10] equity across poverty levels, low levels of education, cultural norms, and disabilities may be more challenging to overcome. Our assessment indicates that large exclusions of a safety-net population in 2015 are a legitimate concern in communication strategies that rely too heavily on mHealth. These findings underscore the CONSORT-EHEALTH recommendation that investigators report web-based recruitment strategies and data-collection methods comprehensively.[17]

Regarding access, our estimates suggest that historical disparities in smartphone ownership are diminishing, but access to Internet capabilities may still be lower among the urban poor compared to the nation as a whole. The Pew Research Center found that 64% of Americans owned a smartphone in 2015 (respondents defined smartphone).[10] In comparison, 87% (95% CI, 75%, 94%) of our study participants owned a text-enabled mobile device and 64% (47%, 78%) owned an Internet-enabled mobile device. However, the 40% (31%, 50%) of our safety-net population with an uninterrupted data plan over the previous year may be lower than the 50% of Americans reporting uninterrupted data plans over their lifetime.[10] The impact of expense-related data plan interruptions is magnified by the 40% of our study population—compared to 15% of Americans—who are dependent on mobile devices for Internet access.[10] The association between Internet connectivity and literacy evokes multiple bidirectional pathways yet to be elucidated. But if mHealth can reduce health disparities, closing the gap in device ownership is only a partial accomplishment, and future work also needs to expand Internet connectivity to allow literacy-enhancing and literacy-naïve technologies to flourish.

This study has limitations. Our study population was a consecutive sample and participation rate was less than 100%. However, we recruited participants into the study the way we may also have approached patients to introduce mHealth options in our clinical settings. Our sampling method proved adequate for our primary goal to explain differences in technology access and engagement using regression analysis. Although our patient population may not directly generalize to many healthcare systems, including other safety-net systems serving regions with variable technology uptake,[18] our findings reflect the capacities and the preferences of the most disadvantaged segments of urban populations. We systematically excluded LEP non-Spanish speakers, but they consisted of less than 5% of inpatients and no outpatients. We did not assess current technology use. Finally, as discussed earlier, access and use of new technologies change rapidly and frequent updates are necessary.

mHealth is a promising tool because it may increase healthcare access, improve care quality, and promote research. All these potential benefits will be obtained with accompanying efforts to reduce healthcare disparities, especially where some technologies themselves are exclusionary.[9] As research of mHealth methods grows, support for patients with IRHL and LEP are still necessary to simultaneously advance our shared goal for equity.

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Medical and Economic Burden of Heparin-Induced Thrombocytopenia: A Retrospective Nationwide Inpatient Sample (NIS) Study

Ranjan Pathak, MD[1]*, Vijaya Raj Bhatt, MBBS[2], Paras Karmacharya, MD[1], Madan Raj Aryal, MD[1], Anthony A. Donato, MD, MHPE[1]

[1]Department of Internal Medicine, Reading Health System, West Reading, Pennsylvania; [2]Division of Hematology-Oncology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska.

In recent years, US hospitals have switched from use of unfractionated heparin to use of low-molecular-weight heparin, which is associated with lower risk of heparin-induced thrombocytopenia (HIT). In the study reported here, we retrospectively searched the Nationwide Inpatient Sample (NIS) for patients who were at least 18 years old and received a diagnosis of HIT between 2009 and 2011. Our goal was to get an updated perspective on the incidence and economic impact of HIT. We calculated the incidence of HIT overall and in subgroups of patients who underwent cardiac, vascular, or orthopedic surgery. We compared characteristics of patients with and without HIT and compared characteristics of patients with HIT with thrombosis (HITT) and HIT patients without thrombosis. Of 98,636,364 hospitalizations, 72,515 (0.07%) involved HIT. Arterial and venous thromboses were identified in 24,880 (34.3%) of HIT cases. Men were slightly more likely to have a HIT diagnosis (50.1%), but women had higher rates of HIT after cardiac surgery (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.26-1.58) and vascular surgery (OR, 1.42; 95% CI, 1.29-1.57). Rates of HIT were 0.53% (95% CI, 0.51%-0.54%) after cardiac surgery, 0.28% (95% CI, 0.28%-0.29%) after vascular surgery, and 0.05% (95% CI, 0.05%-0.06%) after orthopedic surgery. HIT and HITT cases were significantly ($P < 0.001$) more likely than non-HIT cases to be fatal (9.63% and 12.28% vs 2.19%), and they had significantly higher costs and longer inpatient stays. HIT and especially HITT are associated with increased mortality, costs, and length of stay. *Journal of Hospital Medicine* 2017;12:94-97. © 2017 Society of Hospital Medicine

Each year, approximately one-third of all hospitalized medical and surgical patients in the United States (about 12 million patients) are exposed to heparin products for the prevention or treatment of thromboembolism.[1] Although generally safe, heparin can trigger an immune response in which platelet factor 4–heparin complexes set off an antibody-mediated cascade that can result in heparin-induced thrombocytopenia (HIT) and paradoxical arterial and venous thromboses, or heparin-induced thrombocytopenia with thrombosis (HITT). The incidence of HIT appears to be significantly higher with the more immunogenic unfractionated heparin (UFH) (2%-3% if treated for ≥5 days) than with low-molecular-weight heparin (LMWH) (0.2%-0.6%)[2] and is significantly higher in postoperative patients (1%-5%) than in medical patients.[3] Older patients and female patients, especially those who undergo surgery, are thought to be at higher risk.[4] Progression from HIT to HITT can occur in up to 50% of surgical patients,[5] and HITT can significantly increase mortality.[4]

In the United States, LMWH use has increased 5-fold since 2000—an increase attributed to the 2010 release of generic enoxaparin.[6] As US hospitals switch from UFH to LMWH with its significantly lower risk of HIT, up-to-date HIT incidence data may help physicians and payers better understand the impact of the disorder on mortality and hospital length of stay (LOS) for medical patients and subsets of surgical patients and subsequently direct screening efforts to those at highest risk. Therefore, in the present study, we used national data to determine the latest incidence and economic implications of HIT overall and for high-risk surgical groups.

METHODS

In this study, we analyzed data from the Nationwide Inpatient Sample (NIS) database, part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ). The period studied was 2009-2011. We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 289.84, introduced in 2009, to identify patients who were at least 18 years old and had a primary or secondary diagnosis of HIT. Validated Clinical Classifications Software (CCS) was used to identify those who underwent cardiac, vascular, or orthopedic surgery, and ICD-9-CM codes for various thromboses were used to identify those with HITT (Supplemental Figure, Supplemental Table 1). Baseline patient and hospital characteristics were compared using the Pearson's Chi-square test for categorical variables and the Student *t* test for continuous variables (2-sided $P < 0.05$ for statistical significance) (Table 1). We calculated the incidence of HIT overall and for the 3 surgical subgroups and compared the cohorts on their mean hospital LOS, mean hospital charge, and in-hospital mortality (Table 2).

Statistical analysis was performed with Stata Version 13.1

***Address for correspondence and reprint requests:** Ranjan Pathak, MD, Department of Internal Medicine, Reading Health System, 6th Ave & Spruce St, West Reading, PA; Telephone: 484-628-5455; Fax: 484-628-9003; E-mail: ranjanrp@gmail.com

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TABLE 1. Baseline Characteristics of Patients With HIT and HITT

Characteristic	No HIT (n = 98,563,849)	HIT (n = 72,515)	*P*	HIT w/o thrombosis (n = 47,635)	HITT (n = 24,880)	*P*
Mean (SD) age, y	57.29 (20.79)	65.25 (15.64)	<0.001	65.14 (15.91)	65.46 (15.04)	0.32
Female sex	59.62	49.88	<0.001	50.45	48.77	0.08
Race			0.002			0.009
White	68.35	67.05		65.76	69.56	
Black	15.03	17.12		18.24	14.94	
Hispanic	10.57	8.94		9.12	8.59	
Other/unknown	6.05	6.89		6.88	6.91	
Insurance			<0.001			<0.001
Medicare	45.22	63.02		65.34	58.58	
Medicaid	15.45	9.78		9.87	9.62	
Private	29.86	21.22		19.57	24.56	
Self-pay	5.57	3.09		2.66	3.91	
No charge	0.57	0.47		0.42	0.57	
Other	3.33	2.41		2.24	2.76	
Region			0.15			0.07
Northeast	20.05	17.79		18.22	16.96	
Midwest	23.08	21.31		20.77	22.35	
South	38.35	43.10		43.55	42.23	
West	18.52	17.81		17.47	18.46	
Hospital location/teaching status			<0.001			0.21
Rural	12.46	5.10		5.29	4.72	
Urban/nonteaching	41.80	38.68		39.01	38.05	
Urban/teaching	45.75	56.23		55.70	57.23	
Hospital size (number of beds)			<0.001			<0.001
Small (1-49)	12.36	10.44		10.94	9.49	
Medium (50-99)	23.87	20.29		21.12	18.70	
Large (100+)	63.77	69.26		67.93	71.81	

NOTE: Abbreviations: HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis.

(Stata Corp, College Station, TX). Survey commands were used to account for the complex survey design in NIS. Reading Health System's Institutional Review Board determined that our study protocol was exempt.

RESULTS

Of 98,636,364 hospitalizations, 72,515 (0.07%) involved HIT. There were no significant differences in the annual incidence of HIT during the study period (0.06% in 2009, 0.05% in 2010, 0.06% in 2011).

Patients with HIT were older than patients without HIT (mean age, 65.3 vs 57.3 years; $P < 0.001$). HIT was slightly more common in men overall (OR, 1.48; 95% CI, 1.46-1.51), but subgroup analyses revealed women had higher rates of HIT after cardiac surgery (OR, 1.41; 95% CI, 1.26-1.58) and vascular surgery (OR, 1.42; 95% CI, 1.29-1.57), though not after orthopedic surgery (OR, 1.06; 95% CI, 0.89-1.26). The majority of HIT cases were in urban teaching hospitals (56.23%) and in large hospitals, those with at least 325 beds (69.26%). There was no difference in mean age between patients with HITT and patients with HIT without thrombosis (65.46 vs 65.14 years; $P = 0.32$). Although the incidence of HITT did not differ by hospital location or teaching status, HITT cases were more common in hospitals with at least 325 beds (71.81%).

Regarding HIT, the death rate was 4-fold higher for patients with the disorder (9.63%) than for those without it (2.19%); hospital LOS and costs were significantly higher, too (Table 2). In addition, in-hospital mortality was higher ($P < 0.001$) for patients with HITT (12.28%) than for patients with HIT without thrombosis (8.24%); HITT patients' hospital LOS and costs were higher as well. In patients who had cardiac, vascular, or orthopedic surgery, development of HIT was also associated with significantly higher in-hospital mortality, mean hospital LOS, and mean hospital charge. In patients with HITT, deep vein thrombosis (DVT) and pulmonary embolism represented the majority of reported cases (Supplemental Table 2). However, in patients who had cardiac surgery, acute arterial thromboses of coronary and cerebral vessels were more common.

DISCUSSION

In this national database survey, the overall incidence of HIT during the study period 2009-2011 was 0.07%, or 1 in 1350 hospitalized patients. Although earlier studies reported rates as high as 5% for high-risk subgroups of surgical patients,[7] our data are more in line with more recently reported rates: about 0.02% for hospital admissions[8] and from less than 0.1% to 0.4% for patients who received heparin.[9]

TABLE 2. In-Hospital Mortality, Mean Hospital LOS, and Mean Hospital Charge for Patients With HIT and HITT, Overall and in Cardiac, Vascular, and Orthopedic Surgery

Overall	No HIT (n = 98,563,849)	HIT (n = 72,515)	*P*	HIT w/o thrombosis (n = 47,635)	HITT (n =2 4,880)	*P*
In-hospital mortality	2.19%	9.63% (OR 4.75, 95% CI 4.45-5.08)	<0.001	8.24%	12.28% (OR 1.56, 95% CI 1.40-1.74)	<0.001
Mean LOS (days)	4.76 (95% CI 4.71-4.82)	14.07 (95% CI 13.67-14.48)	<0.001	12.80 (95% CI 12.38-13.23)	16.51 (95% CI 15.96-17.06)	<0.001
Mean total hospital charge (USD)	35905 (95% CI 34626-37185)	137401 (95% CI 129369-145433)	<0.001	115456 (95% CI 108251-122661)	179735 (95% CI 168582-190889)	<0.001
	No HIT			HIT (% of total)		*P*
Cardiac surgery	n = 1305639			n = 6888 (0.52%)		
In-hospital mortality	4.31%			14.66% (OR 3.81, 95% CI 3.24-4.49)		<0.001
LOS (days)	9.02 (95% CI 8.81-9.23)			20.44 (19.37-21.52)		<0.001
Mean hospital charge (USD)	145616 (95% CI 138071-153161)			318885 (95% CI 295967-341803)		<0.001
Vascular surgery	n = 3189979			n = 8989 (0.28%)		
In-hospital mortality	2.80%			9.79% (OR 3.77, 95% CI 3.21-4.43)		<0.001
LOS (days)	6.05 (95% CI 5.89-6.20)			17.36 (16.55-18.17)		<0.001
Mean hospital charge (USD)	85929 (95% CI 81879-89979)			214849 (95% CI 198542-231156)		<0.001
Orthopedic surgery	n = 5279871			n = 2795 (0.05%)		
In-hospital mortality	0.52%			2.81% (OR 5.52, 95% CI 3.31-9.25)		<0.001
LOS (days)	4.17 (95% CI 4.10-4.22)			10.17 (95% CI 9.19-11.14)		<0.001
Mean hospital charge (USD)	53297 (95% CI 51387-55207)			104810 (95% CI 94544-115077)		<0.001

NOTE: Abbreviations: CI, confidence interval; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis; LOS, length of stay; OR, odds ratio.

Older studies, which predominantly involved postoperative patients and were conducted when UFH often was the first-line heparin product used, may account for higher rates relative to ours. Of the 3 types of surgeries we evaluated, cardiac surgery had the highest HIT rate (0.5%), consistent with other studies.[4] The higher HIT/HITT rates found for larger urban hospitals in our study might be attributable to increased awareness and testing, availability of hematology consultation, and higher risk of heparin use in this setting, where patients are sicker and cases and procedures more complicated.

Age was an important determinant of HIT risk in our study and in similar large-database series.[4] Whether increased UFH use in the elderly (because of age or kidney disease) was a causative factor in this finding is unknown. In our study, although men and women had a nearly equal incidence of HIT, women had a significantly higher risk of HIT after both cardiac surgery and vascular surgery. Immune-mediated mechanisms that are more common in females may play a causative role in these settings.[10]

Our study results showed HIT associated with increased hospital LOS and an almost 4-fold increase in inpatient mortality and costs. The increased economic burden in HIT cases may be driven by the diagnostic work-up cost and expensive alternative anticoagulation.[11,12] Similarly, compared with HIT without thrombosis, HITT was associated with significantly increased hospital LOS (3.7 days), total hospital charge ($64,279) and mortality (49% increase, to 12.2% from 8.2%), consistent with prior studies.[13] In addition, 34.1% (24,704) of our HIT patients developed at least 1 thrombotic complication, with venous thromboses more common than arterial thromboses, as previously reported.[13] Lower extremity DVT was the most common thrombosis in orthopedic and vascular surgery. However, in cardiac surgery, acute coronary occlusion was the most common thrombotic complication. We postulate that the difference stems from the increased propensity of HIT-related thrombosis to occur in areas of vascular injury.[14]

The strengths of our study include its large size, which increases the generalizability of its results and avoids the biases inherent in small, single-center studies. As with any administrative dataset, the NIS may include coding errors related to underdiagnosis and overdiagnosis (eg, a HIT/HITT diagnosis carried forward from prior episodes). In our study, we inferred the HITT diagnosis in HIT cases with a vascular complication, but we could have missed HIT cases that had not been coded for vascular complications, and we could have overassociated vascular complications that had predated HIT and been treated with heparin. Although HIT and HITT were associated with worse clinical outcomes and increased hospital LOS, it is possible patients who were hospitalized longer had more opportunities for heparin use, and this exposure led to HIT or HITT. The lack of details regarding prior heparin use, including type of heparin (UFH or LMWH), prevented us from inferring the actual risks of individual heparin products.

In conclusion, in cardiac, vascular, and orthopedic surgery, HIT and especially HITT can significantly increase hospital

LOS, inpatient costs, and mortality. Lower extremity DVT and acute coronary artery occlusion are the most common thrombotic complications in these cases. HIT screening strategies that incorporate platelet counts are recommended only in patients at highest risk (>1%), according to the most recent American College of Chest Physicians guidelines, but this recommendation was made on the basis of the high cost of alternative anticoagulants. Given our more recent data regarding the very high costs of HIT and especially HITT, screening strategies with platelet counts may prove more cost-effective. Recent genome-wide studies that found higher rates of HIT in patients with T-cell death–associated gene 8 (*TDAG8*) may help explain sex differences in postoperative patients and identify patients at highest risk so alternative anticoagulants can be used.[15]

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Assessment of Readability, Understandability, and Completeness of Pediatric Hospital Medicine Discharge Instructions

Ndidi I. Unaka, MD, MEd[1]*, Angela Statile, MD, MEd[1], Julianne Haney[1], Andrew F. Beck, MD, MPH[1,2], Patrick W. Brady, MD, MSc[1,3], Karen E. Jerardi, MD, MEd[1]

[1]Division of Hospital Medicine, [2]Division of General and Community Pediatrics, [3]James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

The average American adult reads at an 8th-grade level. Discharge instructions written above this level might increase the risk of adverse outcomes for children as they transition from hospital to home. We conducted a cross-sectional study at a large urban academic children's hospital to describe readability levels, understandability scores, and completeness of written instructions given to families at hospital discharge. Two hundred charts for patients discharged from the hospital medicine service were randomly selected for review. Written discharge instructions were extracted and scored for readability (Fry Readability Scale [FRS]), understandability (Patient Education Materials Assessment Tool [PEMAT]), and completeness (5 criteria determined by consensus). Descriptive statistics enumerated the distribution of readability, understandability, and completeness of written discharge instructions. Of the patients included in the study, 51% were publicly insured. Median age was 3.1 years, and median length of stay was 2.0 days. The median readability score corresponded to a 10th-grade reading level (interquartile range, 8-12; range, 1-13). Median PEMAT score was 73% (interquartile range, 64%-82%; range, 45%-100%); 36% of instructions scored below 70%, correlating with suboptimal understandability. The diagnosis was described in only 33% of the instructions. Although explicit warning signs were listed in most instructions, 38% of the instructions did not include information on the person to contact if warning signs developed. Overall, the readability, understandability, and completeness of discharge instructions were subpar. Efforts to improve the content of discharge instructions may promote safe and effective transitions home. *Journal of Hospital Medicine* 2017;12:98-101. © 2017 Society of Hospital Medicine

The average American adult reads at an 8th-grade level.[1] Limited general literacy can affect health literacy, which is defined as the "degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions."[2,3] Adults with limited health literacy are at risk for poorer outcomes, including overuse of the emergency department and lower adherence to preventive care recommendations.[4]

Children transitioning from hospital to home depend on their adult caregivers (and their caregivers' health literacy) to carry out discharge instructions. During the immediate postdischarge period, complex care needs can involve new or changed medications, follow-up instructions, home care instructions, and suggestions regarding when and why to seek additional care.

The discharge education provided to patients in the hospital is often subpar because of lack of standardization and divided responsibility among providers.[5] Communication of vital information to patients with low health literacy has been noted to be particularly poor,[6] as many patient education materials are written at 10th-, 11th-, and 12th-grade reading levels.[4] Evidence supports providing materials written at 6th-grade level or lower to increase comprehension.[7] Several studies have evaluated the quality and readability of discharge instructions for hospitalized adults,[8,9] and one study found a link between poorly written instructions for adult patients and readmission risk.[10] Less is known about readability in pediatrics, in which education may be more important for families of children most commonly hospitalized for acute illness.

We conducted a study to describe readability levels, understandability scores, and completeness of written instructions given to families at hospital discharge.

METHODS

Study Design and Setting

In this study, we performed a cross-sectional review of discharge instructions within electronic health records at Cincinnati Children's Hospital Medical Center (CCHMC). The study was reviewed and approved by CCHMC's Institutional Review Board. Charts were randomly selected from all hospital medicine service discharges during two 3-month periods of high patient volume: January-March 2014 and January-March 2015.

CCHMC is a large urban academic referral center that is the sole provider of general, subspecialty, and critical pediatric inpatient care for a large geographical area. CCHMC, which has 600 beds, provides cares for many children who live in impoverished settings. Its hospital medicine service

***Address for correspondence and reprint requests:** Ndidi I. Unaka, MD, MEd, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, ML 5018, Cincinnati, OH 45229; Telephone: 513-636-8354; Fax: 513-636-7905; E-mail: ndidi.unaka@cchmc.org

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consists of 4 teams that care for approximately 7000 children hospitalized with general pediatric illnesses each year. Each team consists of 5 or 6 pediatric residents supervised by a hospital medicine attending.

Providers, most commonly pediatric interns, generate discharge instructions in electronic health records. In this nonautomated process, they use free-text or nonstandardized templates to create content. At discharge, instructions are printed as part of the postvisit summary, which includes updates on medications and scheduled follow-up appointments. Bedside nurses verbally review the instructions with families and provide printed copies for home use.

Data Collection and Analysis

A random sequence generator was used to select charts for review. Instructions written in a language other than English were excluded. Written discharge instructions and clinical information, including age, sex, primary diagnosis, insurance type, number of discharge medications, number of scheduled appointments at discharge, and hospital length of stay, were abstracted from electronic health records and anonymized before analysis. The primary outcomes assessed were discharge instruction readability, understandability, and completeness. Readability was calculated with Fry Readability Scale (FRS) scores,[11] which range from 1 to 17 and correspond to reading levels (score 1 = 1st-grade reading level). Health literacy experts have used the FRS to assess readability in health care environments.[12]

Understandability was measured with the Patient Education Materials Assessment Tool (PEMAT), a validated scoring system provided by the Agency for Healthcare Research and Quality.[13] The PEMAT measures the understandability of print materials on a scale ranging from 0% to 100%. Higher scores indicate increased understandability, and scores under 70% indicate instructions are difficult to understand.

Although recent efforts have focused on the development of quality metrics for hospital-to-home transitions of pediatric patients,[14] during our study there were no standard items to include in pediatric discharge instructions. Five criteria for completeness were determined by consensus of 3 pediatric hospital medicine faculty and were informed by qualitative results of work performed at our institution—work in which families noted challenges with information overload and a desire for pertinent and usable information that would enhance caregiver confidence and discharge preparedness.[15] The criteria included statement of diagnosis, description of diagnosis, signs and symptoms indicative of the need for escalation of care (warning signs), the person caregivers should call if worried, and contact information for the primary care provider, subspecialist, and/or emergency department. Each set of discharge instructions was manually evaluated for completeness (presence of each individual component, number of components present, presence of all components). All charts were scored by the same investigator. A convenience sample of 20 charts was evaluated by a different investigator to ensure rating parameters were clear and classification was consistent (defined as perfect agreement). If the primary rater was undecided on a discharge instruction score, the secondary rater rated the instruction, and consensus was reached.

Means, medians, and ranges were calculated to enumerate the distribution of readability levels, understandability scores, and completeness of discharge instructions. Instructions were classified as readable if the FRS score was 6 or under, as understandable if the PEMAT score was under 70%, and as complete if all 5 criteria were satisfied. Descriptive statistics were generated for all demographic and clinical variables.

TABLE 1. Demographic Characteristics of Patients Whose Discharge Instructions Were Reviewed for Readability, Understandability, and Completeness (n = 200)

Characteristic	N (%)
Median (IQR) age, y	3.1 (2.2-8.9)
Female	101 (51)
Public insurance	101 (51)
Most common discharge diagnoses	
Bronchiolitis	56 (28)
Pneumonia	16 (8)
Asthma	11 (5.5)
Acute gastroenteritis	9 (4.5)
Brief resolved unexplained event	8 (4)
Hospital length of stay, d	
1	83 (41)
2	84 (42)
≥3	33 (17)
Number of discharge appointments	
0	110 (55)
1	45 (22.5)
≥2	45 (22.5)
Number of discharge medications	
0	110 (55)
1	45 (22.5)
2-4	79 (39.5)
≥5	47 (23.5)

NOTE: Abbreviation: IQR, interquartile range.

RESULTS

Of the study period's 3819 discharges, 200 were randomly selected for review. Table 1 lists the demographic and clinical information of patients included in the analyses. Median FRS score was 10, indicating a 10th-grade reading level (interquartile range, 8-12; range, 1-13) (Table 2). Only 14 (7%) of 200 discharge instructions had a score of 6 or under. Median PEMAT understandability score was 73% (interquartile range, 64%-82%), and 36% of instructions had a PEMAT score under 70%. No instruction satisfied all 5 of the defined characteristics of complete discharge instructions (Table 2).

DISCUSSION

To our knowledge, this is the first study of the readability, understandability, and completeness of discharge instruc-

TABLE 2. Descriptive Statistics Illustrating Readability, Understandability, and Completeness of Written Discharge Instructions

Outcome	Calculated Value	Interpretation
Readability		
Median FRS score (1-17), (IQR)	10[a] (8-12)	10th-grade reading level (8th-12th grade)
Understandability		
Median PEMAT score (0%-100%)(IQR)	73% (64%-82%)	Score <70% indicates text is difficult to understand
Completeness: number of instructions with:		
Discharge diagnosis	146 (73%)	
Description of diagnosis	66 (33%)	
Explicit warning signs	164 (82%)	
Information on person to contact with concerns	125 (63%)	
Physician contact information	23 (12%)	
All 5 components	0 (0%)	

[a]Score corresponds to grade level.

NOTE: Abbreviations: FRS, Fry Readability Scale; IQR, interquartile range; PEMAT, Patient Education Materials Assessment Tool.

tions in a pediatric population. We found that the majority of discharge instruction readability levels were 10th grade or higher, that many instructions were difficult to understand, and that important information was missing from many instructions.

Discharge instruction readability levels were higher than the literacy level of many families in surrounding communities. The high school dropout rates in Cincinnati are staggering; they range from 22% to 64% in the 10 neighborhoods with the largest proportion of residents not completing high school.[16] However, such findings are not unique to Cincinnati; low literacy is prevalent throughout the United States. Caregivers with limited literacy skills may struggle to navigate complex health systems, understand medical instructions and anticipatory guidance, perform child care and self-care tasks, and understand issues related to consent, medical authorization, and risk communication.[17]

Although readability is important, other factors also correlate with comprehension and execution of discharge tasks.[18] Information must be understandable, or presented in a way that makes sense and can inform appropriate action. In many cases in our study, instructions were incomplete, despite previous investigators' emphasizing caregivers' desire and need for written instructions that are complete, informative, and inclusive of clearly outlined contingency plans.[15,19] In addition, families may differ in the level of support needed after discharge; standardizing elements and including families in the development of discharge instructions may improve communication.[8]

This study had several limitations. First, the discharge instructions randomly selected for review were all written during the winter months. As the census on the hospital medicine teams is particularly high during that time, authors with competing responsibilities may not have had enough time to write effective discharge instructions then. We selected the winter period in order to capture real-world instructions written during a busy clinical time, when providers care for a high volume of patients. Second, caregiver health literacy and English-language proficiency were not assessed, and information regarding caregivers' race/ethnicity, educational attainment, and socioeconomic status was unavailable. Third, interrater agreement was not formally evaluated. Fourth, this was a single-center study with results that may not be generalizable.

In conclusion, discharge instructions for pediatric patients are often difficult to read and understand, and incomplete. Efforts to address these communication gaps—including educational initiatives for physician trainees focused on health literacy, and quality improvement work directed at standardization and creation of readable, understandable, and complete discharge instructions—are crucial in providing safe, high-value care. Researchers need to evaluate the relationship between discharge instruction quality and outcomes, including unplanned office visits, emergency department visits, and readmissions.

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Student Perceptions of High-Value Care Education in Internal Medicine Clerkships

Amit Pahwa, MD[1]*, Danelle Cayea, MD, MS[2], Amanda Bertram, MS[1], Ariella Apfel, MPH[1], Chad Miller, MD[3], Nick Van Wagoner, MD, PhD[4], James Willig, MD, MSPH[4], Reena Karani, MD, MHPE[5], Bimal Ashar, MD, MBA[1]

[1]Division of General Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Division of Geriatric Medicine and Gerontology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana; [4]Division of Infectious Disease, University of Alabama School of Medicine, Birmingham, Alabama; [5]Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York, New York.

During internal medicine (IM) clerkships, course directors are responsible for ensuring that medical students attain basic competency in patient management through use of risk–benefit, cost–benefit, and evidence-based considerations.[1] However, the students' primary teachers—IM residents and attendings—consistently role-model high-value care (HVC) perhaps only half the time.[2] The inconsistency may have a few sources, including unawareness of the costs of tests and treatments ordered and little formal training in HVC.[3-5] In addition, the environment at some academic institutions may reward learners for performing tests that may be unnecessary.[6]

We conducted a study to assess medical students' perceptions of unnecessary testing and the adequacy–inadequacy of HVC instruction, as well as their observations of behavior that may hinder the practice of HVC during the IM clerkship.

METHODS

When students completed their third-year IM clerkships at The Johns Hopkins University School of Medicine, the Icahn School of Medicine at Mount Sinai, the University of Alabama at Birmingham School of Medicine, and the Tulane University School of Medicine, we sent them a recruitment email asking them to complete an anonymous survey regarding their clerkship experiences with HVC. The clerkships' directors, who collaborated on survey development, searched the literature to quantify behavior thought to decrease the practice of HVC. The survey was tested several times with different learners and faculty to increase response process validity.

The SurveyMonkey online platform was used to administer the survey. Students were given 1 week after the end of their clerkship to complete the survey. Data were collected for the period October 2013 to December 2014. Each student was offered a $10 gift certificate for survey completion. Each institution received exempt approval from its institutional review board.

***Address for correspondence and reprint requests:** Amit Pahwa, MD, Division of General Internal Medicine, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Nelson 215, Baltimore, MD 21287; Telephone: 410-502-2128; Fax: 410-502-0923; E-mail: apahwa1@jhmi.edu

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Survey respondents were divided into those who perceived HVC education as adequate and those who perceived it as inadequate. Chi-square tests were performed with Stata Version 12 (College Station, TX) to determine whether a student's perception of HVC education being adequate or inadequate was significantly associated with the other survey questions.

RESULTS

Of 577 eligible students, 307 (53%) completed the survey. About 83% of the respondents reported noticing the ordering of laboratory or radiologic tests they considered unnecessary, and a majority (81%) of those students noticed this activity at least once a week. Overall, 51% of the respondents thought their HVC education was inadequate. Significantly more of the students who perceived their HVC education as inadequate were uncomfortable bringing an unnecessary test to the attention of the ward team, rarely discussed costs, and rarely observed team members being praised for forgoing unnecessary tests (Table). Two significant associations were found: between institution attended and perceived adequacy–inadequacy of HVC education and between institution and frequency of cost discussions.

Most (78.5%) students thought an HVC curriculum should be added to the IM clerkship, and 34.5% thought the HVC curriculum should be incorporated into daily rounds. In regards to additions to the clerkship curriculum, most students wanted to round with phlebotomy (29%) or discuss costs of testing on patients (26%).

Students attributed the ordering of unnecessary tests and treatments to several factors: residents investigating "interesting diagnoses" (46%), teams practicing defensive medicine (43%), consultants making requests (40%), attendings investigating "interesting diagnoses" (27%), and patients making requests (8%).

DISCUSSION

About 51% of the students thought their HVC education was inadequate, and about 83% noticed unnecessary testing. Our study findings reaffirm those of a single-site study in which 93% of students noted unnecessary testing.[7]

In this study, many students perceived HVC education as inadequate and reported wanting HVC principles added to their training and an HVC curriculum incorporated into

TABLE. Student Observations of Behavior That May Hinder Practice of High-Value Care[a]

Observation	n (%) Inadequate (n = 121)	Appropriate (n = 116)	*P*
How comfortable or uncomfortable do you feel bringing to the attention of the ward team that a lab/radiologic test is unnecessary?			<0.01
Completely uncomfortable/Uncomfortable	74 (61.2)	51 (44.0)	
Neutral	11 (9.1)	8 (6.9)	
Comfortable/Completely comfortable	36 (29.8)	57 (49.1)	
How often were costs of tests/Rxs discussed at any time when caring for patients?			<0.001
Never/Rarely	68 (56.2)	28 (24.1)	
Sometimes	39 (32.2)	41 (35.3)	
Often/Frequently	14 (11.6)	47 (40.5)	
How often was a team member *praised* for *not* ordering a lab/radiologic test that was unnecessary?			<0.001
Never/Rarely	80 (66.1)	52 (44.8)	
Sometimes	37 (30.6)	39 (33.6)	
Often/Frequently	4 (3.3)	25 (21.6)	
How often was a team member *guided* to order more testing on a patient even though it seemed unnecessary?			0.35
Never/Rarely	44 (36.4)	53 (45.7)	
Sometimes	54 (44.6)	44 (37.9)	
Often/Frequently	23 (19.0)	19 (16.4)	

[a]Responses of students who reported that education in high-value cost-conscious care was inadequate or appropriate.

daily rounds. Students who perceived HVC education as inadequate were significantly less comfortable bringing an unnecessary test to the attention of the ward team and noticed less discussion about costs and less praise for avoiding unnecessary tests. One institution had a significantly higher proportion of students perceiving their HVC education as adequate and noticing more discussions about test costs. This institution was the only one that incorporated discussions about test costs into its curriculum during the study period—which may account for its students' perceptions.

This study had a few limitations. First, as the survey was administered after the IM clerkships, students' responses may have been subject to recall bias. We minimized this bias by allowing 1 week for survey completion. Second, given the 53% response rate, there may have been response bias. However, one institution's demographics showed no significant differences between responders and nonresponders with respect to age, sex, ethnicity, or type of degree. Third, students' understanding of what tests and treatments are necessary and unnecessary may be relatively underdeveloped, given their training level. One study found that medical students with minimal clinical experience were able to identify unnecessary tests and treatments, but this study has not been validated at other institutions.[7]

Efforts to increase HVC education and practice have focused on residents and attendings, but our study findings reaffirm that HVC training is much needed and wanted in undergraduate medical education. Studies are needed to test the effectiveness of HVC curricula in medical school and the ability of these curricula to give students the tools they need to practice HVC.

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A Shocking Diagnosis

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

Anbazhagan Prabhakaran, MD[1]*, Gurpreet Dhaliwal, MD[2,3], Christopher Robert-James Schilf, MD[1], George H. Caughey, MD[2,3], James Pile, MD[4]

[1]Medicine Institute, Cleveland Clinic, Cleveland, Ohio; [2]Department of Medicine, University of California, San Francisco, California; [3]Medical Service, San Francisco VA Medical Center, San Francisco, California; [4]Department of Medicine, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio.

A 75-year-old man was brought by ambulance to the emergency department (ED) after the acute onset of palpitations, lightheadedness, and confusion. His medical history, provided by his wife, included osteoarthritis and remote cholecystectomy. He was not a smoker but drank 2 to 4 cans of beer daily. His medications were aspirin 162 mg daily and naproxen as needed. There was no history of bruising, diarrhea, melena, or bleeding.

Palpitations may represent an arrhythmia arising from an ischemic or alcoholic cardiomyopathy. Mental status changes usually have metabolic, infectious, structural (eg, hemorrhage, tumor), or toxic causes. Lightheadedness and confusion could occur with arrhythmia-associated cerebral hypoperfusion or a seizure. Daily alcohol use could cause confusion through acute intoxication, thiamine or B_{12} deficiency, repeated head trauma, or liver failure.

The patient's systolic blood pressure (BP) was 60 mm Hg, heart rate (HR) was 120 beats per minute (bpm), and oral temperature was 98.4°F. Rousing him was difficult. There were no localizing neurologic abnormalities, and the rest of the physical examination findings were normal. Point-of-care blood glucose level was 155 mg/dL. Blood cultures were obtained and broad-spectrum antibiotics initiated. After fluid resuscitation, BP improved to 116/87 mm Hg, HR fell to 105 bpm, and the patient became alert and oriented. He denied chest pain, fever, or diaphoresis.

The patient's improvement with intravenous (IV) fluids makes cardiogenic shock unlikely but does not exclude an underlying compensated cardiomyopathy that may be predisposing to arrhythmia. Hypotension, tachycardia, and somnolence may represent sepsis, but the near normalization of vital signs and mental status shortly after administration of IV fluids, the normal temperature, and the absence of localizing signs of infection favor withholding additional antibiotics. Other causes of hypotension are hypovolemia, medication effects, adrenal insufficiency, anaphylaxis, and autonomic insufficiency. There was no reported nausea, vomiting, diarrhea, bleeding, polyuria, or impaired oral intake to support hypovolemia, though the response to IV fluids suggests hypovolemia may still be playing a role.

White blood cell (WBC) count was 15,450/μL with a normal differential; hemoglobin level was 15.8 g/dL; and platelet count was 176,000/μL. Electrolytes, liver function tests, cardiac enzymes, and urinalysis were normal. Electrocardiogram showed sinus tachycardia with premature atrial complexes and no ST-segment abnormalities. Radiograph of the chest and computed tomography scan of the head were normal. Echocardiogram showed moderate left ventricular hypertrophy with a normal ejection fraction and no valvular abnormalities. Exercise nuclear cardiac stress test was negative for ischemia. Blood cultures were sterile. The patient quickly became asymptomatic and remained so during his 3-day hospitalization. There were no arrhythmias on telemetry. The patient was discharged with follow-up scheduled with his primary care physician.

The nonlocalizing history and physical examination findings, normal chest radiograph and urinalysis, absence of fevers, negative blood cultures, and quick recovery make infection unlikely, despite the moderate leukocytosis. Conditions that present with acute and transient hypotension and altered mental status include arrhythmias, seizures, and reactions to drugs or toxins. Given the cardiac test results, a chronic cardiomyopathy seems unlikely, but arrhythmia is still possible. Continuous outpatient monitoring is required to assess the palpitations and the frequency of the premature atrial complexes.

***Address for correspondence and reprint requests:** Anbazhagan Prabhakaran, MD, Medicine Institute, M2 Annex, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195; Telephone: 216-538-9022; Fax: 216-444-8530; E-mail: prabhak@ccf.org

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Two days after discharge, the patient suddenly became diaphoretic and lost consciousness while walking to the bathroom. He was taken to the ED, where his BP was 90/60 mm Hg and HR was 108 bpm. Family members reported that he had appeared flushed during the syncopal episode, showed no seizure activity, and been unconscious for 15 to 20 minutes. The patient denied chest pain, dyspnea, fever, bowel or bladder incontinence, focal weakness, slurred speech, visual changes, nausea or vomiting either before or after the episode. Physical examination revealed a tongue laceration and facial erythema; all other findings were normal. In the ED, there was an asymptomatic 7-beat run of nonsustained ventricular tachycardia, and the hypotension resolved after fluid resuscitation. The patient now reported 2 similar syncopal episodes in the past. The first occurred in a restaurant 6 years earlier, and the second occurred 3 years later, at which time he was hospitalized and no etiology was found.

The loss of consciousness is attributable to cerebral hypoperfusion. Hypotension has 3 principal categories: hypovolemic, cardiogenic, and distributive. With syncopal episodes recurring over several years, hypovolemia seems unlikely. Given the palpitations and ventricular tachycardia, it is reasonable to suspect a cardiogenic cause. Although his heart appears to be structurally normal on echocardiogram, genetic, electrophysiologic, or magnetic resonance imaging (MRI) testing will occasionally reveal an unsuspected substrate for arrhythmia.

The recurring yet self-limited nature, diaphoresis, flushing, and facial erythema suggest a non-sepsis distributive cause of hypotension. It is possible the patient is recurrently exposed to a toxin (eg, alcohol) that causes both flushing and dehydration. Flushing disorders include carcinoid syndrome, pheochromocytoma, drug reaction with eosinophilia and systemic symptoms (DRESS), and mastocytosis. Carcinoid syndrome is characterized by bronchospasm and diarrhea and, in some cases, right-sided valvulopathy, all of which are absent in this patient. Pheochromocytoma is associated with orthostasis, but patients typically are hypertensive at baseline. DRESS, which may arise from nonsteroidal anti-inflammatory drug (NSAID) or aspirin use, can cause facial erythema and swelling but is also characterized by liver, renal, and hematologic abnormalities, none of which was demonstrated. Furthermore, DRESS typically does not cause hypotension. Mastocytosis can manifest as isolated or recurrent anaphylaxis.

It is important to investigate antecedents of these syncopal episodes. If the earlier episodes were food-related—one occurred at a restaurant—then deglutition syncope (syncope precipitated by swallowing) should be considered. If an NSAID or aspirin was ingested before each episode, then medication hypersensitivity or mast cell degranulation (which can be triggered by these medications) should be further examined. Loss of consciousness lasting 20 minutes without causing any neurologic sequelae is unusual for most causes of recurrent syncope. This feature raises the possibility that a toxin or mediator might still be present in the patient's system.

Serial cardiac enzymes and electrocardiogram were normal. A tilt-table study was negative. The cortisol response to ACTH (cosyntropin) stimulation was normal. The level of serum tryptase, drawn 2 days after syncope, was 18.4 ng/dL (normal, <11.5 ng/dL). Computed tomography scan of chest and abdomen was negative for pulmonary embolism but showed a 1.4×1.3-cm hypervascular lesion in the tail of pancreas. The following neuroendocrine tests were within normal limits: serum and urine catecholamines; urine 5-hydroxyindoleacetic acid (5-HIAA); and serum chromogranin A, insulin, serotonin, vasoactive intestinal polypeptide (VIP), and somatostatin (Table 1). The patient remained asymptomatic during his hospital stay and was discharged home with appointments for cardiology follow-up and endoscopic ultrasound-guided biopsy of the pancreatic mass.

Pheochromocytoma is unlikely with normal serum and urine catecholamine levels and normal adrenal images. The differential diagnosis for a pancreatic mass includes pancreatic carcinoma, lymphoma, cystic neoplasm, and neuroendocrine tumor. All markers of neuroendocrine excess are normal, though elevations can be episodic. The normal 5-HIAA level makes carcinoid syndrome unlikely. VIPomas are associated with flushing, but the absence of profound and protracted diarrhea makes a VIPoma unlikely.

As hypoglycemia from a pancreatic insulinoma is plausible as a cause of episodic loss of consciousness lasting 15 minutes or more, it is important to inquire if giving food or drink helped resolve previous episodes. The normal insulin

TABLE 1. Neuroendocrine Tests

Test	Value	Normal Range
Serum catecholamine		
Dopamine	<20	0-20 pg/mL
Norepinephrine	266	80-520 pg/mL
Epinephrine	<10	10-200 pg/mL
24-hour urine catecholamine		
Dopamine	57	52-480 µg/24 h
Norepinephrine	13	15-100 µg/24 h
Epinephrine	<6	2-24 µg/24 h
Chromogranin A	3.6	1.9-15 ng/mL
24-hour urine 5-HIAA	4.0	0.0-10.0 mg/24 h
Insulin	8.2	1-24 µIU/mL
Serotonin	66	≤230 ng/mL
Vasoactive intestinal polypeptide	25	<75 pg/mL
Somatostatin	25	≤30 pg/mL

NOTE: Abbreviation: 5-HIAA, 5-hydroxyindoleacetic acid.

level reported here is of limited value, because it is the combination of insulin and C-peptide levels at time of hypoglycemia that is diagnostic. The normal glucose level recorded during one of the earlier episodes and the hypotension argue against hypoglycemia.

The elevated tryptase level is an indicator of mast cell degranulation. Tryptase levels are transiently elevated during the initial 2 to 4 hours after an anaphylactic episode and then normalize. An elevated level many hours or days later is considered a sign of mast cell excess. Although there is no evidence of the multi-organ disease (eg, cytopenia, bone disease, hepatosplenomegaly) seen in patients with a high systemic burden of mast cells, mast cell disorders exist on a spectrum. There may be a focal excess of mast cells confined to one organ or an isolated mass.

The same day as discharge, the patient's wife drove them to the grocery store. He remained in the car while she shopped. When she returned, she found him confused and minimally responsive with subsequent brief loss of consciousness. He was taken to an ED, where he was flushed and hypotensive (systolic BP, 60 mm Hg) and tachycardic. Other examination findings were normal. After fluid resuscitation he became alert and oriented. WBC count was 20,850/μL with 89% neutrophils, hemoglobin level was 14.6 g/dL, and platelet count was 168,000/μL. Serum lactate level was 3.7 mmol/L (normal, <2.3 mmol/L). Chest radiograph was normal. He was treated with broad-spectrum antibiotic therapy and admitted to the hospital. Blood and urine cultures were sterile. Fine-needle aspiration of the pancreatic mass demonstrated nonspecific inflammation. Four days after admission (3 days after pancreatic mass biopsy) the patient developed palpitations, felt unwell, and had marked flushing of the face and trunk, with concomitant BP of 90/50 mm Hg and HR of 140 bpm.

The salient features of this case are recurrent hypotension, tachycardia, and flushing. Autonomic insufficiency, to which elderly patients are prone, causes hemodynamic perturbations but rarely flushing. The patient does not have diabetes mellitus, Parkinson disease, or another condition that puts him at risk for dysautonomia. Pancreatic neuroendocrine tumors secrete mediators that lead to vasodilation and hypotension but are unlikely given the clinical and biochemical data.

The patient's symptoms are consistent with anaphylaxis, though prototypical immunoglobulin E (IgE)–mediated anaphylaxis is usually accompanied by urticaria, angioedema, and wheezing, which have been absent during his presentations. There are no clear food, pharmacologic, or environmental precipitants.

Recurrent anaphylaxis can be a manifestation of mast cell excess (eg, cutaneous or systemic mastocytosis). A markedly elevated tryptase level during an anaphylactic episode is consistent with mastocytosis or IgE-mediated anaphylaxis. An elevated baseline tryptase level days after an anaphylactic episode signals increased mast cell burden. There may be a reservoir of mast cells in the bone marrow. Alternatively, the hypervascular pancreatic mass may be a mastocytoma or a mast cell sarcoma (missed because of inadequate sampling or staining).

The lactic acidosis likely reflects global tissue hypoperfusion from vasodilatory hypotension. The leukocytosis may reflect WBC mobilization secondary to endogenous corticosteroids and catecholamines in response to hypotension or may be a direct response to the release of mast cell–derived mediators of inflammation.

The patient was treated with diphenhydramine and ranitidine. Serum tryptase level was 46.8 ng/mL (normal, <11.5 ng/mL), and 24-hour urine histamine level was 95 μg/dL (normal, <60 μg/dL). Bone marrow biopsy results showed multifocal dense infiltrative aggregates of mast cells (>15 cells/aggregate), which were confirmed by CD117 (Kit) and tryptase positivity (Figure). Mutation analysis for Kit Asp816Val, which is present in 80% to 90% of patients with mastocytosis, was positive. He fulfilled the 2008 World Health Organization criteria for systemic mastocytosis (Table 2). Prednisone, histamine inhibitors, and montelukast were prescribed. Six months later, magnetic resonance imaging of the abdomen showed no change in the pancreatic mass, which was now characterized as a possible splenule. The patient had no additional episodes of flushing or syncope over 2 years.

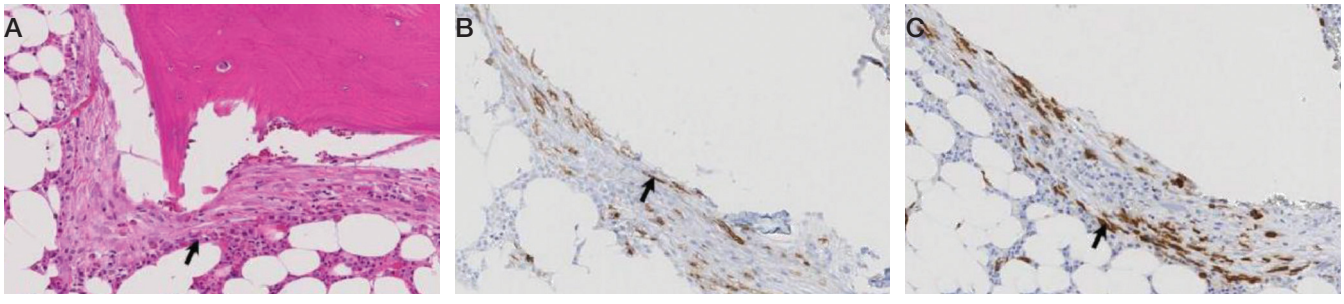

FIG. Bone marrow biopsy histopathology. (A) Dense aggregate of >15 abnormal spindled mast cells (arrow); similar aggregates are multifocal throughout biopsy (hematoxylin-eosin stain). Immunohistochemical stains for CD117 (Kit) (B) and tryptase (C) confirm that spindled cells within aggregates are mast cells (arrows). Mast cells also aberrantly express CD2 and CD25 (not shown).

TABLE 2. World Health Organization Criteria for Diagnosis of Systemic Mastocytosis[a]

Major
• Multifocal dense mast-cell infiltrate (>15 mast cells per infiltrate) in bone marrow and/or extracutaneous organs
Minor
• Presence of Asp816Val Kit mutation in bone marrow, peripheral blood, or extracutaneous tissue
• Expression of CD117 (Kit) with CD2 and/or CD25 in mast cells of bone marrow
• >25% atypical or spindle-shaped mast cells
• Serum tryptase >20 ng/mL

[a]Diagnosis requires either 1 major criterion + 1 minor criterion or 3 minor criteria.

DISCUSSION

Cardiovascular collapse (hypotension, tachycardia, syncope) in an elderly patient prompts clinicians to focus on life-threatening conditions, such as acute coronary syndrome, pulmonary embolus, arrhythmia, and sepsis. Each of these diagnoses was considered early in the course of this patient's presentations, but each was deemed unlikely as it became apparent that the episodes were self-limited and recurrent over years. Incorporating flushing into the diagnostic problem representation allowed the clinicians to focus on a subset of causes of hypotension.

Flushing disorders may be classified by whether they are mediated by the autonomic nervous system (wet flushes, because they are usually accompanied by diaphoresis) or by exogenous or endogenous vasoactive substances (dry flushes).[1] Autonomic nervous system flushing is triggered by emotions, fever, exercise, perimenopause (hot flashes), and neurologic conditions (eg, Parkinson disease, spinal cord injury, multiple sclerosis). Vasoactive flushing precipitants include drugs (eg, niacin); alcohol (secondary to cutaneous vasodilation, or acetaldehyde particularly in people with insufficient acetaldehyde dehydrogenase activity)[2]; foods that contain capsaicin, tyramine, sulfites, or histamine (eg, eating improperly handled fish can cause scombroid poisoning); and anaphylaxis. Rare causes of vasoactive flushing include carcinoid syndrome, pheochromocytoma, medullary thyroid carcinoma, VIPoma, and mastocytosis.[2]

Mastocytosis is a rare clonal disorder characterized by the accumulation of abnormal mast cells in the skin (cutaneous mastocytosis), in multiple organs (systemic mastocytosis), or in a solid tumor (mastocytoma). Urticaria pigmentosa is the most common form of cutaneous mastocytosis; it is seen more often in children than in adults and typically is associated with a maculopapular rash and dermatographism. Systemic mastocytosis is the most common form of the disorder in adults.[3] Symptoms are related to mast cell infiltration or mast cell mediator–related effects, which range from itching, flushing, and diarrhea to hypotension and anaphylaxis. Other manifestations are fatigue, urticaria pigmentosa, osteoporosis, hepatosplenomegaly, bone pain, cytopenias, and lymphadenopathy.[4]

Systemic mastocytosis can occur at any age and should be considered in patients with recurrent unexplained flushing, syncope, or hypotension. Eighty percent to 90% of patients with systemic mastocytosis have a mutation in Kit,[5] a transmembrane tyrosine kinase that is the receptor for stem cell factor. The Asp816Val mutation leads to increased proliferation and reduced apoptosis of mast cells.[3,6,7] Proposed diagnostic algorithms[8-11] involve measurement of serum tryptase levels and examination of bone marrow. Bone marrow biopsy and testing for the Asp816Val Kit mutation should be considered in patients with modestly elevated baseline tryptase levels (11.5-20 ng/mL) if clinical findings are consistent with mastocytosis.[12]

The primary goals of treatment are managing mast cell–mediated symptoms and, in advanced cases, achieving cytoreduction. Alcohol can trigger mast cell degranulation in indolent systemic mastocytosis and should be avoided. Mast cell–mediated symptoms are managed with histamine blockers, leukotriene antagonists, and mast cell stabilizers.[12] Targeted therapy with tyrosine kinase inhibitors (eg, imatinib) in patients with transmembrane Kit mutation (eg, Phe522Cys, Lys509Ile) associated with systemic mastocytosis has had promising results.[13,14] However, this patient's Asp816Val mutation is in the Kit catalytic domain, not the transmembrane region, and therefore would not be expected to respond to imatinib. A recent open-label trial of the multikinase inhibitor midostaurin demonstrated resolution of organ damage, reduced bone marrow burden, and lowered serum tryptase levels in patients with advanced systemic mastocytosis.[15] Interferon, cladribine, and high-dose corticosteroids are prescribed in patients for whom other therapies have been ineffective.[8]

The differential diagnosis is broad for both hypotension and for flushing, but the differential diagnosis for *recurrent hypotension and flushing* is limited. Recognizing that flushing was an essential feature of this patient's hypotensive condition, and not an epiphenomenon of syncope, allowed the clinicians to focus on the overlap and make a shocking diagnosis.

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Impact of Patient-Centered Discharge Tools: A Systematic Review

Karen Okrainec, MD, MSc[1-3]*, Davina Lau, BSc[4], Howard B. Abrams, MD[1-3], Shoshanna Hahn-Goldberg, PhD[3], Ronak Brahmbhatt, MBBS, MPH[3], Tai Huynh, MBA[3], Kenneth Lam, MD[2], Chaim M. Bell, MD, PhD[2,4-6]

[1]University Health Network, Toronto, Ontario, Canada; [2]Department of Medicine, University of Toronto, Ontario, Canada; [3]OpenLab, University Health Network, Toronto, Ontario, Canada; [4]Samuel Lunenfeld Research Institute/Mount Sinai Hospital, Toronto, Ontario, Canada; [5]University of Toronto Institute of Health Policy, Management and Evaluation, Ontario, Canada; [6]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada.

BACKGROUND: Patient-centered discharge tools provide an opportunity to engage patients, enhance patient understanding, and improve capacity for self-care and postdischarge outcomes.

PURPOSE: To review studies that engaged patients in the design or delivery of discharge instruction tools and that tested their effect among hospitalized patients.

DATA SOURCES: We conducted a search of 12 databases and journals from January 1994 through May 2014, and references of retrieved studies.

STUDY SELECTION: English-language studies that tested discharge tools meant to engage patients were selected. Studies that measured outcomes after 3 months or without a control group or period were excluded.

DATA EXTRACTION: Two independent reviewers assessed the full-text papers and extracted data on features of patient engagement.

DATA SYNTHESIS: Thirty articles met inclusion criteria, 28 of which examined educational tools. Of these, 13 articles involved patients in content creation or tool delivery, with only 6 studies involving patients in both. While many of these studies (10 studies) demonstrated an improvement in patient comprehension, few studies found improvement in patient adherence despite their engagement. A few studies demonstrated an improvement in self-efficacy (2 studies) and a reduction in unplanned visits (3 studies).

CONCLUSIONS: Improving patient engagement through the use of media, visual aids, or by involving patients when creating or delivering a discharge tool improves comprehension. However, further studies are needed to clarify the effect on patient experience, adherence, and healthcare utilization postdischarge. Better characterization of the level of patient engagement when designing discharge tools is needed given the heterogeneity found in current studies. *Journal of Hospital Medicine* 2017;12:110-117. © 2017 Society of Hospital Medicine

Patient-centered care, defined by the Institute of Medicine as "health care that establishes a partnership among practitioners, patients, and their families to ensure that decisions respect patients' wants, needs and preferences and that patients have the education and support they need to make decisions and participate in their own care," has been recognized as an important factor in improving care transitions after discharge from the hospital.[1] Previous efforts to improve the discharge process for hospitalized patients and reduce avoidable readmissions have focused on improving systems surrounding the patient, such as by increasing the availability of outpatient follow-up or standardizing communication between the inpatient and outpatient care teams.[1,2] In fact, successful programs such as Project BOOST and the Care Transitions Interventions™ provide healthcare institutions with a "bundle" of evidence-based transitional care guidelines for discharge: they provide postdischarge transition coaches, assistance with medication self-management, timely follow-up tips, and improved patient records in order to improve postdischarge outcomes.[3,4] Successful interventions, however, may not provide more services, but also engage the patient in their own care.[5,6] The impact of engaging the patient in his or her own care by providing patient-friendly discharge instructions alone, however, is unknown.

A patient-centered discharge may use tools that were designed with patients, or may involve engaging patients in an interactive process of reviewing discharge instructions and empowering them to manage aspects of their own care after leaving the hospital. This endeavour may lead to more effective use of discharge instructions and reduce the need for additional or more intensive (and costly) interventions. For example, a patient-centered discharge tool could include an educational intervention that uses the "teach-back" method, in which patients are asked to restate in their own words what they thought they heard, or in which staff use additional media or a visual design tool meant to enhance comprehension of discharge instructions.[6,7] Visual aids and the use of larger fonts are particularly useful design elements for improving comprehension among non-English speakers and patients with low health literacy, who tend to have poorer recall of instructions.[8-10] What may constitute essential design elements to include in a discharge instruction tool, however, is not clear.

Moreover, whether the use of discharge tools with a specif-

***Address for correspondence and reprint requests:** Karen Okrainec, MD, MSc, Toronto Western Hospital, University Health Network, 399 Bathurst Street, 8EW-432E, Toronto, Ontario, Canada M5T2S8; Telephone: 416-603-5800 x2141; Fax: 416-603-6495; E-mail: karen.okrainec@uhn.ca

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ic focus on patient engagement may improve postdischarge outcomes is not known. Particularly, the ability of patient-centered discharge tools to improve outcomes beyond comprehension such as self-management, adherence to discharge instructions, a reduction in unplanned visits, and a reduction in mortality has not been studied systematically. The objective of this systematic review was to review the literature on discharge instruction tools with a focus on patient engagement and their impact among hospitalized patients.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was followed as a guideline for reporting throughout this review.[11]

Data Sources

A literature search was undertaken using the following databases from January 1994 or their inception date to May 2014: Medline, Embase, SIGLE, HTA, Bioethics, ASSIA, Psych Lit, CINAHL, Cochrane Library, EconLit, ERIC, and BioMed Central. We also searched relevant design-focused journals such as *Design Issues, Journal of Design Research, Information Design Journal, Innovation, Design Studies*, and *International Journal of Design*, as well as reference lists from studies obtained by electronic searching. The following key words and combination of key words were used with the assistance of a medical librarian: patient discharge, patient-centered discharge, patient-centered design, design thinking, user based design, patient education, discharge summary, education. Additional search terms were added when identified from relevant articles (Appendix).

Inclusion Criteria

We included all English-language studies with patients admitted to the hospital irrespective of age, sex, or medical condition, which included a control group or time period and which measured patient outcomes within 3 months of discharge. The 3-month period after discharge is often cited as a time when outcomes could reasonably be associated with an intervention at discharge.[2]

Exclusion Criteria

Studies that did not have clear implementation of a patient-centered tool, a control group, or those whose tool was used in the emergency department or as an outpatient were excluded. Studies that included postdischarge tools such as home visits or telephone calls were excluded unless independent effects of the predischarge interventions were measured. Studies with outcomes reported after 3 months were excluded unless outcomes before 3 months were also clearly noted.

All searches were entered into Endnote and duplicates were removed. A 2-stage inclusion process was used. Titles and abstracts of articles were first screened for meeting inclusion and exclusion criteria by 1 reviewer. A second reviewer independently checked a 10% random sample of all the abstracts that met the initial screening criteria. If the agreement to exclude studies was less than 95%, criteria were reviewed before checking the rest of the 90% sample. In the second stage, 2 independent reviewers examined paper copies of the full articles selected in the first stage. Disagreement between reviewers was resolved by discussion or a third reviewer if no agreement could be reached.

Data Analysis and Synthesis

The following information was extracted from the full reference: type of study, population studied, control group or time period, tool used, and outcomes measured. Based on the National Health Care Quality report's priorities and goals on patient and/or family engagement during transitions of care, educational tools were further described based on method of teaching, involvement of the care team, involvement of the patient in the design or delivery of the tool, and/or the use of visual aids.[12] All primary outcomes were classified according to 3 categories: improved knowledge/comprehension, patient experience (patient satisfaction, self-management/efficacy such as functional status, both physical and mental), and health outcomes (unscheduled visits or readmissions, adherence with medications, diet, exercise, or follow-up, and mortality).

No quantitative pooling of results or meta-analysis was done given the variability and heterogeneity of studies reviewed. However, following guidelines for Effect Practice and Organisation of Care (EPOC) Risk of Bias criteria,[13] studies that had a higher risk of bias such as uncontrolled before-after studies or studies with only 1 intervention or control site (historical controls, eg) were excluded from the final review because of the difficulties in attributing causation. Only primary outcomes were reported in order to minimize type II errors.

RESULTS

Our search revealed a total of 3699 studies after duplicates had been removed (Figure). A total of 714 references were included after initial review by title and abstract and 30 studies after full-text review. Agreement on a 10% random sample of all abstracts and full text was 79% (κ=0.58) and 86% (κ=0.72), respectively. Discussion was needed for fewer than 100 references, and agreement was subsequently reached for 100%.

There were 22 randomized controlled trials and 8 nonrandomized studies (5 nonrandomized controlled trials and 3 controlled before-after studies). Most of these studies were conducted in the United States (13/30 studies), followed by other European countries (5 studies), and the United Kingdom (4 studies). A large number of studies were conducted among patients with cardiovascular disease or risk factors (10 studies), followed by postsurgical patients such as coronary artery bypass graft surgery or orthopaedic surgery (5 studies). Five of 30 studies were conducted among individuals older than 65 years. Most studies excluded patients who did not speak English or the country's official language; only 3

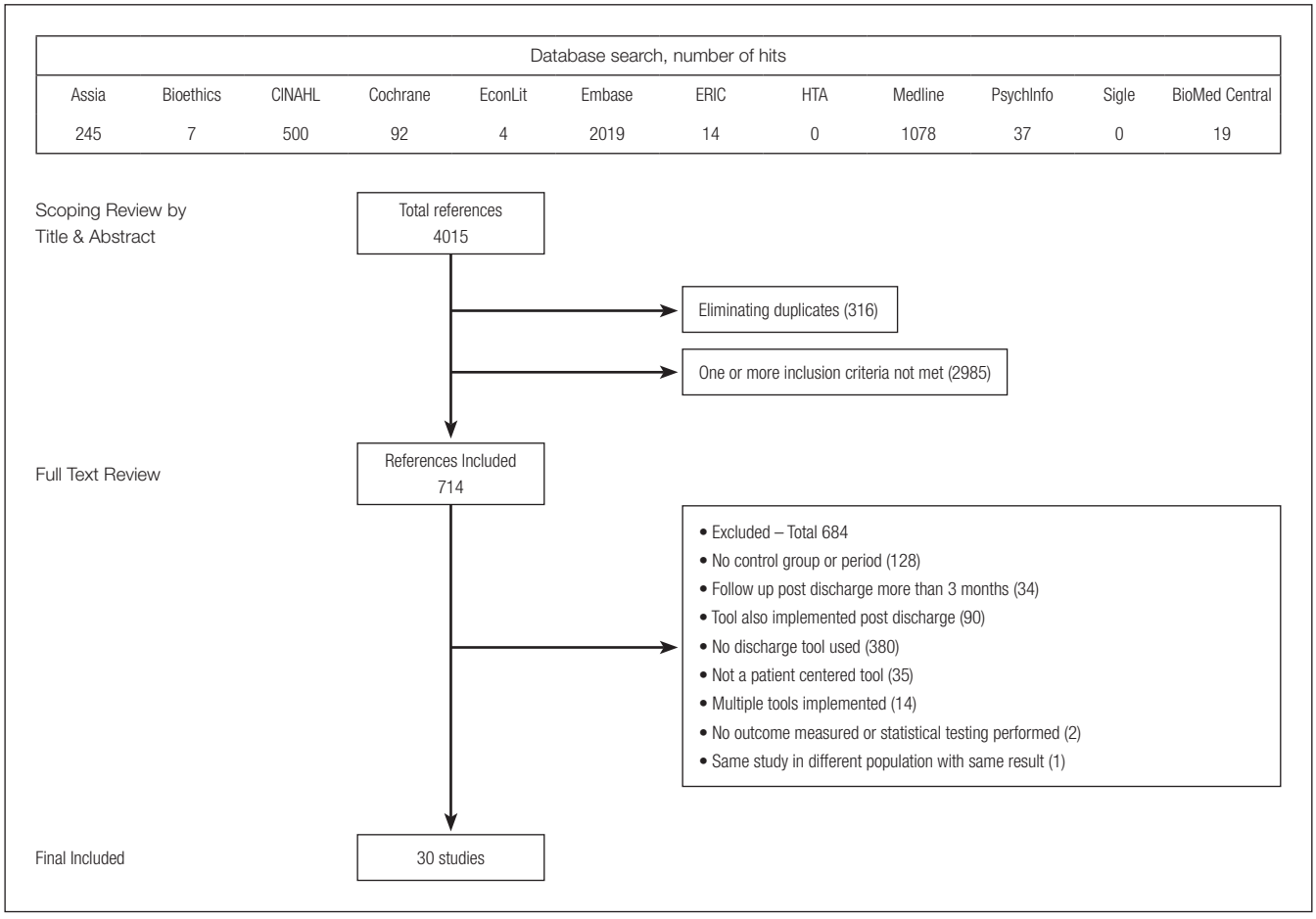

FIG. Flow diagram of the inclusion process.

studies included patients with limited literacy, patients who spoke other languages, or caregivers if the patients could not communicate.

Most studies tested the impact of educational discharge interventions (28 of 30 studies) (Table 1). Quite often, it was a member of the research team who carried out the patient education. Only 3 studies involved multiple members of the care team in designing or reviewing the discharge tool with the patient. Almost half (12 studies) targeted multiple aspects of postdischarge care, including medications and side effects, signs and symptoms to consider, plans for follow-up, dietary restrictions, and/or exercise modifications. Many (19 studies) provided education using one-on-one teaching in association with a discharge tool, accompanied by a written handout (13 studies), audiotape (2 studies), or video (3 studies). While 13 studies had patients involved in creating what content was discussed and 14 studies had patients involved in the delivery of the tool, only 6 studies had patients involved in both design and delivery of the tool. Nine studies also used visual aids such as pictures, larger font, or use of a tool enhanced for patients with language barriers or limited health literacy.

Among all 30 studies included, 16 studies tested the impact of their tool on comprehension postdischarge, with 10 studies demonstrating an improvement among patients who had received the tool (Table 2). Five studies evaluated healthcare utilization outcomes such as readmission, length of stay, or physician visits after discharge and 2 studies found improvements. Twelve studies also studied the impact on adherence with medications, diet, exercise, or follow-up instructions postdischarge. However, only 4 of these 12 studies showed a positive impact. Only 2 studies tested the impact on a patient's ability to self-manage once at home, and both studies reported positive statistical outcomes. Few studies measured patient experience (such as patient satisfaction or improvement in self-efficacy) or mortality postdischarge.

DISCUSSION/CONCLUSION

Our systematic review found 30 studies that engaged patients during the design or the delivery of a discharge instruction tool and that tested the effect of the tool on postdischarge outcomes.[6-10,14–38] Our review suggests that there is sufficient evidence that patient-centered discharge tools improve comprehension. However, evidence is currently insufficient to determine if patient-centered tools improve adherence with discharge instructions. Moreover, though limited studies show promising results, more studies are needed to determine if patient engagement improves self-efficacy and

TABLE 1. Summary of Discharge Educational Instruction Tools Being Tested (N = 28)

Study	N and Study Population	Content of Intervention Tool	Method of Teaching	Additional Use of Media[a]	Degree of Patient Centeredness: Patient Involved in Design/Content	Degree of Patient Centeredness: Patient Involved in Process/Delivery	Degree of Patient Centeredness: Visual Aids[b]
Randomized Controlled Trials							
Mahler et al., 1999[17]	215 adults post-CABG	Expected symptoms, instructions regarding exercise, diet, when to seek attention	None	Video	Custom-made using descriptions of 4 actual CABG patients	No	No
Morice et al., 2001[8]	80 Adults with asthma	Pathophysiology, triggers, review of medications, self-management plan, when to seek care	One-on-one	Written	Use of self-management plan	Use of teach-back	Illustrations in written booklet
Osman et al., 2002[6]	280 Adults with acute asthma	Medications, warning symptoms	One-on-one	Written	Use of self-management plan	Patient's own management plan using template	No
Gwadry-Sridhar et al., 2005[21]	134 Adults with heart failure	Medication compliance, diet, and lifestyle recommendations	Multidisciplinary	No	Incorporate personalized feedback in education	No	No
Cordasco et al., 2009[7]	210 Adults with low literacy	Medication schedule	None	Written	Tool developed with patient feedback	No	Picture- and icon-based for low literacy, English and Spanish
Kommuri et al., 2012[25]	265 Adults with heart failure	Medication compliance, diet and lifestyle recommendations, when to seek attention	One-on-one	Written	No	No	Written guidelines provided for low literacy
Al-Rashed et al., 2002[18]	89 Elderly	Medications and compliance	One-on-one	No	No	Use of teach-back	No
Press et al., 2014[38]	120 Adults with COPD or asthma	Medication technique	One-on-one	No	No	Use of teach-back	No
Legrain et al., 2011[10]	665 Elderly	Medication review, self-management, communication with outpatient physician	One-on-one	No	Incorporated patient priorities into treatment plan	Education assessed the patient's health priorities	No
Lysack et al., 2005[28]	40 Adults postorthopedic surgery receiving rehab	Rehabilitation exercises	None	Video	No	Patients assessed for understanding through demonstration	No
Ho et al., 2009[22]	200 Postpartum	Information regarding postpartum depression	One-on-one	Written	No	No	No
Pereles et al., 1996[30]	107 Elderly	Self-medication program	Multidisciplinary	No	No	Increasing responsibility based on patient's successful compliance	No
Williford et al., 1995[36]	60 Adults from rehab and acute care	Medication review	One-on-one	No	No	Patient assessed for understanding	No

Continued on page 114

healthcare utilization after discharge.

A major limitation of current studies is the variability in the level of patient engagement in tool design or delivery. Patients were involved in the design mostly through targeted development of a discharge management plan and the delivery by encouraging them to ask questions. Few studies involved patients in the design of the tool such that patients were responsible for coming up with content that was of interest to them. The few that did, often with the additional use of video media, demonstrated significant outcomes. Only a minority of studies used an interactive process to assess understanding such as "teach-back" or maximize patient comprehension such as visual aids. Even fewer studies engaged patients in both developing the discharge tool and providing discharge instructions.

Several previous studies have demonstrated that most complications after discharge are the result of ineffective communication, which can be exacerbated by lack of fluency in English or by limited health literacy.[2,39-43] As a result, poor understanding of discharge instructions by patients and their caregivers can create an important care gap.[44] Therefore, the use of patient-centered tools to engage patients at discharge in their own care is needed. How to engage patients consistently and effectively is perhaps less evident, as demonstrated in this review of the literature in which different levels of patient engagement were found. Many of the tools tested placed attention on patient education, sometimes in the context of bundled care along with home visits or follow-up, all of which can require extensive resources and time. Providing patients with information that the patients themselves state is of value may be the easiest refinement to a discharge educational tool, although this was surprisingly

TABLE 1. Summary of Discharge Educational Instruction Tools Being Tested (N = 28) *(continued)*

Study	N and Study Population	Content of Intervention Tool	Method of Teaching	Additional Use of Media[a]	Degree of Patient Centeredness		
					Patient Involved in Design/Content	Patient Involved in Process/ Delivery	Visual Aids[b]
Haerem et al., 2000[9]	50 Adults with acute coronary syndrome	Medications, lifestyle, risk factors	One-on-one	Audio	Personalized content included	No	No
Jenkins et al., 1996[24]	123 Families of children with burns	Burn care, optional sections	Multidisciplinary	Written	Content tailored to patients based on age group	No	Written at grade school level with numerous diagrams
Shieh et al., 2010[33]	59 Parents of premature newborns	Need for screening, follow-up, emergency management, medication, and other	One-on-one	Written	Mothers used to develop content	Mothers had to demonstrate skill	Photos included
Sabariego et al., 2013[32]	213 Adults with stroke undergoing rehab	Functional difficulties	Group	No	Patients independently identified select topics for discussion	Patients encouraged to identify personal solutions	No
Hoffmann et al., 2007[23]	138 Adults with stroke	Ranges from risk factors, management of complications, treatment	One-on-one	Written	Content and design tailored	No	Attention to font and layout, use of illustrations
Whitby et al., 2007[35]	588 Adults postsurgery	Signs and symptoms of surgical site infection	One-on-one	Written	No	No	Pictorial education
Nonrandomized Controlled Studies							
Eshah, 2013[20]	104 Adults with acute coronary syndrome	Signs, symptoms, diet, lifestyle related to ischemic heart disease	One-on-one	No	No	Perceived barriers and benefits discussed with each patient and questions addressed.	No
Reynolds, 2009[31]	146 Adults postsurgery	Pain management and follow-up	One-on-one	Written	No	No	No
Drenth-van Maanen et al., 2013[19]	85 Elderly	Medications	One-on-one	No	No	No	No
Steinberg et al., 1996[34]	50 Adults with organ transplant	Transplant-specific signs, symptoms of complication, medications, diet/exercise and follow-up	One-on-one	Video	Videos developed using patient testimonials	No	No
Lucas, 1998[27]	115 Adults from medical and cardiology wards	Medications	One-on-one	No	No	No	No
Moore, 1996[29]	82 Adults post-CABG	Expected experiences during recovery and instructions for coping	None	Audio	No	No	No
Zernike et al., 1998[37]	40 Adults with hypertension	Risk factors (lifestyle)	One-on-one	Written	Relevance verified through pilot interviews	Interactive process	No
Louis-Simonet et al., 2004[26]	809 Adults on medical ward with ≥1 medication	Medications	One-on-one	Written	No	Clarification of patients treatment plan and questions	Attention to use of nonmedical terms

[a]Written handouts, audiotape, or videos.

[b]Use of pictograms, large font, translated materials, or materials devised for limited literacy.

NOTE: Abbreviation: CABG, coronary artery bypass grafting.

uncommon.[6,9,10,17,23,33,37] Only 2 studies were found that engaged patients in the initial stage of design of the discharge tool, by incorporating information of interest to them.[23,32] For example, a study testing the impact of a computer-generated written education package on poststroke outcomes designed the information by asking patients to identify which topics they would like to receive information about (along with the amount of information and font size).[23] Secondly, although most of the discharge tools reviewed included the use of one-on-one teaching and the use of media such as patient handouts, these tools were often used in such a way that patients were passive recipients. In fact, studies that used additional video media that incorporated personalized content were the most likely to demonstrate positive outcomes.[17,34] The next level of patient engagement may therefore be to involve the patient as an interactive partner when delivering the tool in order to empower patients to self-care. For example, 1 study designed a structured education program by first assessing lifestyle risk factors related to hypertension that were modifiable along with preconceived notions through open-ended questions during a one-on-one interview.[37] Patients were subsequently educated on any knowledge deficits regarding the management of their lifestyle. Another level of patient engagement may be to use visual aids during discussions, as a well-known complement to verbal instructions.[45,46] For example, in a controlled study

that randomized a ward of elderly patients with 4 or more prescriptions to predischarge counseling, the counseling session aimed to review reasons for their prescriptions along with corresponding side effects, doses, and dosage times with the help of a medicine reminder card. Other uses of visual aid tools identified in our review included the use of pictograms or illustrations or, at minimum, attention to font size.[7,8,16,29,33,35] In the absence of a visual aid, asking the patient to repeat or demonstrate what was just communicated can be used to assess the amount of information retained.[18,33]

An important result discovered in our review of the literature was also the lack of studies that tested the impact of discharge tools on usability of discharge information once at home. Conducting an evaluation of the benefits to patients after discharge can help objectify vague outcomes like health gains or qualify benefits in patient's views. This might also explain why many studies with documented patient engagement at the time of discharge were able to demonstrate improvements in comprehension but not adherence to instructions. Although patients and caregivers may understand the information, this comprehension does not necessarily mean they will find the information useful or adhere to it once at home. For example, in 1 study, patients discharged with at least 1 medication were randomized to a structured discharge interview during which the treatment plan was reviewed verbally and questions clarified along with a visually enhanced treatment card.[26] Although knowledge of medications increased, no effect was found on adherence at 1 week postdischarge. However, use of the treatment card at home was not assessed. Similarly, another study tested the effect of an individualized video of exercises and failed to find a difference in patient adherence at 4 weeks.[28] The authors suggested that the lack of benefit may have been because patients were not using the video once at home. This is in contrast to 2 studies that involved patients in their own care by requiring them to request their medication as part of a self-medication tool predischarge.[16,30] Patients were engaged in the process such that increasing independence was given to patients based on their demonstration of understanding and adherence to their treatment while still in the hospital, a learning tool that can be applied once at home. Feeling knowledgeable and involved, as others have suggested, may be the intermediary outcomes that led to improved adherence.[47] It is also possible that adherence to discharge instructions may vary based on complexity of the information provided, such that instructions focusing solely on medication use may require less patient engagement than discharge instructions that include information on medications, diet, exercise modifications, and follow-up.[48]

Our review has a few limitations. Previous systematic reviews have demonstrated that bundled discharge interventions that include patient-centered education have a positive effect on outcomes postdischarge.[2,5] However, we sought to describe and study the individual and distinct impact of patient engagement in the creation and delivery of discharge tools on outcomes postdischarge. We hoped that this may provide others with key information regarding elements of patient engagement that were particularly useful when designing a new discharge tool. The variability of the studies we identified, however, made it difficult to ascertain what level of patient engagement is required to observe improvements in health outcomes. It is also possible that a

TABLE 2. Early Postdischarge Outcomes Measured Among Studies (N = 30)

Outcome	N	N (%) With Impact Demonstrated	Study
Knowledge/comprehension	16	10 (63)	Louis-Simonet et al., 2004,[26a] Zernike et al., 1998,[37a] Reynolds, 2009,[31] Steinberg et al., 1996,[34a] Morice et al., 2001,[8a] Kommuri et al., 2005,[25a] Al-Rashed et al., 2002,[18a] Pereles et al., 1996,[30] Williford et al., 1995,[36b] Lowe et al., 1995,[16a] Haerem et al., 2000,[9a] Jenkins et al., 1996,[24a] Shieh et al., 2010,[33] Hoffmann et al., 2007,[23] Manning et al., 2007,[14] Perera et al., 2012[15]
Patient Experience			
Patient satisfaction	4	2 (50)	Lysack et al., 2005,[28] Hoffmann et al., 2007,[23a] Manning et al., 2007,[14] Osman et al., 2002[6a]
Usefulness of information	0	0	—
Functional status: self-efficacy (physical)	2	2 (100)	Moore, 1996,[29a] Sabariego et al., 2013[32a]
Functional status: mental (including behavior)	6	2 (33)	Eshah, 2013,[20a] Mahler et al., 1999,[17] Moore et al., 1996,[29] Ho et al., 2009,[22a] Pereles et al., 1996,[30] Shieh et al., 2010[33]
Health Outcomes			
Unplanned visits/ readmissions/LOS	5	2 (40)	Lucas, 1998,[27] Osman et al., 2002,[6] Gwadry-Sridhar et al., 2005,[21] Al-Rashed et al., 2002,[18a] Legrain et al., 2011[10a]
Adherence[c]	12	4 (33)	Louis-Simonet et al., 2004,[26] Drenth-van Maanen et al., 2013,[19] Gwadry-Sridhar et al., 2005,[21] Mahler et al., 1999,[17a] Cordasco et al., 2009,[7] Al-Rashed et al., 2002,[18] Press et al., 2014,[38] Lysack et al., 2005,[28] Pereles et al., 1996,[30a] Williford et al., 1995,[36b] Lowe et al., 1995,[16a] Manning et al., 2007[14]
Mortality	1	1	Gwadry-Sridhar et al., 2005[21d]

[a]Significant findings in this study.

[b]Significant differences found among subgroup of population.

[c]Medication, diet, exercise, or follow-up.

[d]Combined with readmission.

NOTE: Abbreviations: CHF, congestive heart failure; LOS, length of stay.

higher level of patient engagement may have been used but not described in the studies we reviewed. As only primary outcomes were included, we may have underestimated the effect of patient-centered discharge tools on outcomes that were reported as secondary outcomes. As we were interested in reviewing as many studies of patient-centered discharge tools as possible, we did not assess the quality of the studies and cannot comment on the role of bias in these studies. However, we excluded studies with study designs known to have the highest risk of bias. Lastly, we also cannot comment on whether patient-centered tools may have an effect on outcomes more than 3 months after a hospital discharge. However, several studies included in this review suggest a sustained effect beyond this time period.[8,25,32,37]

Patient-centered discharge tools in which patients were engaged in the design or the delivery were found to improve comprehension of but not adherence with discharge instructions. The perceived lack of improved adherence may be due to a lack of studies that measured the usefulness and utilization of information for patients once at home. There was also substantial variability in the extent of patient involvement in designing the style and content of information provided to patients at discharge, as well as the extent of patient engagement when receiving discharge instructions. Future studies would benefit from detailing the level of patient engagement needed in designing and delivery of discharge tools. This information may lead to the discovery of barriers and facilitators to utilization of discharge information once at home and lead to a better understanding of the patient's journey from hospital to home and onwards.

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Screening for Depression in Hospitalized Medical Patients

Waguih William IsHak, MD, FAPA[1–3*], Katherine Collison, PhD Candidate[1,4], Itai Danovitch, MD, MBA[1], Lili Shek, MD[5], Payam Kharazi, PsyD[1], Tae Kim, DO Candidate[1,6], Karim Y. Jaffer, MD Candidate[1,7], Lancer Naghdechi, DO Candidate[1,6], Enrique Lopez, PsyD[1], Teryl Nuckols, MD, MSHS[8]

[1]Cedars-Sinai Medical Center, Department of Psychiatry and Behavioral Neurosciences, Los Angeles, California; [2]Cedars-Sinai Medical Center, Department of Health Sciences, Los Angeles, California; [3]David Geffen School of Medicine at UCLA, Los Angeles, California; [4]Purdue University, West Lafayette, Indiana; [5]Cedars-Sinai Medical Center, Department of Internal Medicine, Los Angeles, California; [6]Western University, Los Angeles, California; [7]Cairo University School of Medicine, Cairo, Egypt; [8]Cedars-Sinai Medical Center, Division of General Internal Medicine, Los Angeles, California.

Depression among hospitalized patients is often unrecognized, undiagnosed, and therefore untreated. Little is known about the feasibility of screening for depression during hospitalization, or whether depression is associated with poorer outcomes, longer hospital stays, and higher readmission rates. We searched PubMed and PsycINFO for published, peer-reviewed articles in English (1990-2016) using search terms designed to capture studies that tested the performance of depression screening tools in inpatient settings and studies that examined associations between depression detected during hospitalization and clinical or utilization outcomes. Two investigators reviewed each full-text article and extracted data. The prevalence of depression ranged from 5% to 60%, with a median of 33%, among hospitalized patients. Several screening tools identified showed high sensitivity and specificity, even when self-administered by patients or when abbreviated versions were administered by individuals without formal training. With regard to outcomes, studies from several individual hospitals found depression to be associated with poorer functional outcomes, worse physical health, and returns to the hospital after discharge. These findings suggest that depression screening may be feasible in the inpatient setting, and that more research is warranted to determine whether screening for and treating depression during hospitalization can improve patient outcomes. *Journal of Hospital Medicine* 2017;12:118-125. © 2017 Society of Hospital Medicine

In our current healthcare system, pressure to provide cost- and time-efficient care is immense. Inpatient care often focuses on assessing the patient's presenting illness or injury and treating that condition in a manner that gets the patient on their feet and out of the hospital quickly. Because depression is not an indication for hospitalization so long as active suicidality is absent, inpatient physicians may view it as a problem best managed in the outpatient setting. Yet both psychosocial and physical factors associated with depression put patients at risk for rehospitalization.[1] Furthermore, hospitalization represents an unrecognized opportunity to optimize both mental and physical health outcomes.[2]

Indeed, poor physical and mental health often occur together. Depressed inpatients have poorer outcomes, increased length of stay, and greater vulnerability to hospital readmission.[3,4] Among elderly hospitalized patients, depression is particularly common, especially in those with poor physical health, alcoholism,[5] hip fracture, and stroke.[6] Yet little is known about how often depression goes unrecognized, undiagnosed, and, therefore, untreated.

The US Preventive Services Task Force (USPSTF) recommends screening for depression in the general adult population, including pregnant and postpartum women, and further suggests that screening should be implemented "with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up."[2] The USPSTF guidelines do not distinguish between inpatient and outpatient settings. However, the preponderance of evidence for screening comes from outpatient care settings, and little is known about screening among inpatient populations.[7]

This study had 2 objectives. First, we sought to examine the performance of depression screening tools in inpatient settings. If depression screening were to become routine in hospital settings, screening tools would need to be sensitive and specific as well as brief and suitable for self-administration by patients or for administration by nurses, resident physicians, or hospitalists. It is also important to consider administration by mental health professionals, who may be best trained to administer such tests. We, therefore, examined 3 types of studies: (1) studies that tested a self-administered screening instrument, (2) studies that tested screening by individuals without formal training, and (3) studies that compared screening tools administered by mental health professionals. Second, we sought to describe associations between depression and clinical or utilization outcomes among hospitalized patients.

METHODS

We adhered to recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement,[8,9] including designing the analysis before performing

***Address for correspondence and reprint requests:** Waguih William IsHak, MD, FAPA, 8730 Alden Drive, Thalians E-132, Los Angeles, CA 90048; Telephone: 310-423-3515; Fax: 310-423-3947; E-mail: waguih.ishak@cshs.org

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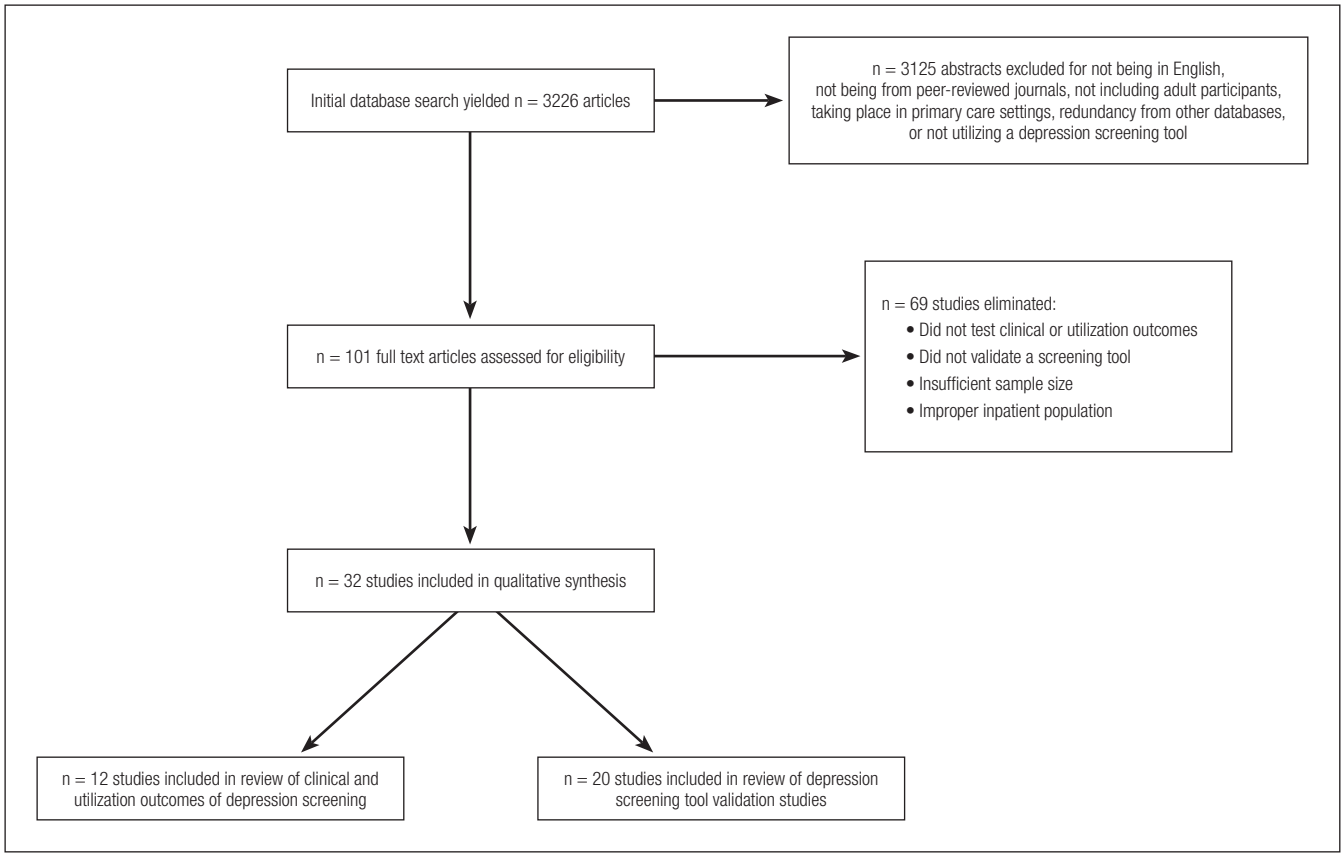

FIG. PRISMA diagram of studies for inclusion.

the review. However, we did not post a protocol in an online registry, formally assess study quality, or perform a meta-analysis.

Data Sources and Searches

We searched PsycINFO and PubMed databases for articles published between 1990 and 2016 (as of July 31, 2016). In PubMed, 2 search term strings were used to capture studies of depression screening tools in inpatient settings. The first used the advanced search option to exclude studies related to primary care settings or children and adolescents, and the second used MeSH terms to ensure that a wide variety of studies were included. Specific search terms are included in the Appendix. A similar search was conducted in the PsycINFO database and these search terms are also included in the Appendix.

Study Selection

Articles were eligible if they were published in English in peer-reviewed journals, included at least 20 adults hospitalized for nonpsychiatric reasons, and described the use of at least 1 measure of depression. The studies must have either tested the validity of a depression screening tool or examined the association between depression screening and clinical or utilization outcomes. Two investigators reviewed each title, abstract, and full-text article to determine eligibility, then reached a consensus on which studies to include in this review.

Data Extraction

Two investigators reviewed each full-text article to extract information related to study design, population, and outcomes regarding screening tool analysis or clinical results. From articles that assessed the performance of depression screening tools, we extracted information related to the nature and application of the index test, the nature and application of the reference test, the prevalence of depression, and the sensitivity and specificity of the index test compared with the reference test. For articles that focused on the association between depression screening and clinical or utilization outcomes, the data on relevant clinical outcomes included symptom severity, quality of life, and daily functioning, whereas the data on utilization outcomes included length of stay, readmission, and the cost of care.

RESULTS

Altogether, the search identified 3226 records. After eliminating duplicates and abstracts not suitable for inclusion (Figure), 101 articles underwent full-text review and 32 were found to be eligible. Of these, 12 focused on the association between depression and clinical or utilization outcomes, while 20 assessed the performance of depression screening tools.

Depression Screening Tools

Table 1 describes the index and reference instruments as well as methods of administration, the prevalence of depression,

TABLE 1. Studies That Have Tested Screening Instruments in Inpatient Settings

	Study Population			Index Test(s)		Reference Test					
Study	Population and Setting	Inclusion Criteria	Exclusion Criteria	Instrument (Minimum Positive Score)	Method of Administration	Instrument	Method of Administration	Prevalence of Depression	Sensitivity of Index Test	Specificity of Index Test	Other Measures of Index Test Performance
Index Test Self-Administered by Patient											
Le Fevre et al., 1999[10]	79 patients admitted to a hospice unit, United Kingdom	Able to complete tests	Serious illness, confusion, delirium	HADS (20)	Completed by patient	CIS-R	Investigating psychiatrist	29%	77%	85%	AUC 0.92
Lloyd-Williams et al., 2000[11]	100 inpatients in hospice or oncology ward for at least 48 h, England	Age 18-70, English-speaking, prognosis of ≤6 months, able to complete tests	On antidepressant, brain metastases, or prognosis ≤1 week	EPDS (13)	Completed by patient	PSE	First author of paper, blinded	22%	81%	79%	PPV 53%; NPV 94%
Amadori et al., 2011[12]	188 randomly selected geriatric inpatients, Germany	Not specified	Not specified	GDS-4 (1/4)	Completed by patient	GDS-15	Completed by patient	44%	76%	86%	—
Diez-Quevedo et al., 2001[13]	1003 inpatients, 1 university hospital, Spain	Age 18-74, medical and surgical patients	Substance dependence, or admitted to psychiatry or obstetrics	PHQ-9 in Spanish (5/9)	Completed by patient	BDI	Completed by patient	42%	84%	92%	—
Young et al., 2015[14]	105 inpatients from cardiology and cardiac surgery step-down units	Age ≥19, cardiac inpatient, able to complete tests	Presence of dementia or delirium	Single item on depression from STOP-D (4)	Completed by patient	HADS	Completed by patient	Not reported	91%	85%	—
Index Test Administered by Individuals Without Formal Training											
Loke et al., 1996[15]	102 consecutive patients admitted to 2 geriatric wards, Western Australia	English-literate, MMSE ≥24/30	Not specified	BASDEC (7) SCL-5 (10)	Medical house officer or research geriatrician	GMS	Blinded research psychiatrist	22%	BASDEC: 91% SCL-5: 77%	BASDEC: 85% SCL-5: 74%	AUC BASDEC: 0.88 SCL-5: 0.77
Shah et al., 1998[16]	50 patients from geriatric inpatient medicine ward, London	All patients admitted to a specific geriatric ward team	Severe cognitive impairment	mDSS (3)	Charge nurse scores based on clinical observation	BAS	Trained interviewer	38%	63%	58%	PPV: 48% NPV: 72%
Payne et al., 2007[17]	167 inpatients in palliative care unit, Ireland	Age ≥18, MMSE ≥24	Actively dying, dysphagia, deaf	2 items on depressed mood and anhedonia (yes on both)	Specialist palliative care registrars	DSM-IV	Formal psychiatric interview by study author	25.7%	90.7%	67.7%	PPV: 49.4% NPV: 95.5%
Rinaldi et al., 2003[18]	60 patients in acute geriatric ward, Italy	Age >65	MMSE score indicating cognitive impairment	GDS-5 (2) GDS-15	Geriatrician	DSM-IV	Geriatrician with experience in depression	48.3%	GDS-5: 97% GDS-15: 90%	GDS-5: 74% GDS-15: 81%	PPV GDS-5: 74% GDS-15: 81% NPV GDS-5: 96% GDS-15: 89%
McGuire et al., 2013[19]	101 patients from cardiac step-down units, United States	Age >18, acute coronary syndrome, English speaking	MMSE ≤24, psychiatric diagnosis other than depression or anxiety, or taking psychotropic medications	PHQ-2 (3, scale 0-6) PHQ-9 (10, scale 0-27)	Staff nurses assigned to patients	Depression Interview and Structured Hamilton	Advanced practice nurse	23%	PHQ-2: 95.6% PHQ-9: 95.6%	PHQ-2: 71.4% PHQ-9: 72.3%	AUC PHQ-2: 0.912 PHQ-9: 0.926

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and the sensitivity and specificity of the index instruments relative to the reference instruments. Across the 20 studies, the prevalence of depression ranged from 15% to 60%, with a median of 34%.[10–29] This finding may reflect different methods of screening or variation among diverse hospitalized populations. Many of the studies excluded patients with cognitive impairment or communication barriers.

The included studies tested a wide range of unique instruments, and compared them with diverse reference standards. Five studies examined instruments that were self-administered by patients[10–14]; 9 studies assessed instruments administered by nurses, physicians, or research staff members

TABLE 1. Studies That Have Tested Screening Instruments in Inpatient Settings *(continued)*

	Study Population			Index Test(s)		Reference Test					
Study	Population and Setting	Inclusion Criteria	Exclusion Criteria	Instrument (Minimum Positive Score)	Method of Administration	Instrument	Method of Administration	Prevalence of Depression	Sensitivity of Index Test	Specificity of Index Test	Other Measures of Index Test Performance
Furlanetto et al., 2005[20]	155 adults in medical wards in university hospital, Rio de Janeiro	Not specified	Discharge expected within 72 h, severe cognitive impairment	BDI-SF (10)	Blinded research assistant	Clinical Interview Schedule (detects moderate to severe depression)	Psychiatrist	Not reported	100%	83.1%	PPV: 59.6% NPV: 100%
Heidenblut et al., 2014[21]	331 patients from 3 geriatric inpatient units, Germany	MMSE ≥15	Aphasia, delirium, psychotic disorders	DIA-S (3.5) GDS-15 (5.5)	Blinded trained interviewer	MADRS	Clinical psychologist	45.6%	DIA-S: 82%; GDS-15: 79%	DIA-S: 79% GDS15: 71%	AUC DIA-S: 0.88 GDS-15: 0.82
Pantilat et al., 2012[22]	162 inpatients with palliative care consultations at large academic center, United States	Age >65, English-speaking	(None)	Depressed mood in past 24 h: NRS (7, scale 0-10), Categorical (mild or worse)	Research assistant	GDS-15	Research assistant	20%	NRS: 37.5% Categorical: 21.9% (article also reports other cut points)	NRS: 80.3% Categorical: 68.8% (article also reports other cut points)	—
Adshead et al., 1992[23]	72 elderly medical inpatients in general hospital, United Kingdom	Cognitively intact patients who could understand English and read large print	Not specified	BASDEC (7) and GDS-30 (14)	Lay interviewer	Formal psychiatric interview	Psychiatrist	33%	BASDEC: 71% GDS-30: 71%	BASDEC: 88% GDS-30: 88%	BASDEC and GDS-30 PPV: 74% BASDEC and GDS-30 NPV: 86%
Index Test Administered by Mental Health Professionals											
Singh et al., 2008[24]	20 randomly chosen, HIV-positive antiretroviral-naïve, inpatients, South Africa	CD4 count <200 cells/mm^3, age <18, no delirium	Not specified	CES-D (16)	Trained psychology counselor	DSM-IV	Psychiatrist	60%	91%	44%	—
Bonin-Guillaume et al., 2007[25]	165 inpatients from different geriatric units, France	Age ≥65	Severe hepatic, renal, cardiac, or neurologic disease, or neuroleptic use	RRS (10)	Trained neuropsychologist	DSM-IV	Interview by geriatrician trained in psychogeriatrics	43%	79%	80%	AUC: 0.86
Rybarczyk et al., 1995[26]	50 consecutive patients admitted to inpatient rehabilitation service	Recent CVA, NCSE ≥25	Not specified	SIDI (17) CES-D (26)	Psychiatrist or psychiatry residents, psychology graduate students	Interview and self-rating scales	Psychiatrist	34%	SIDI: 94% CES-D: 82%	SIDI: 71% CES-D: 65%	—
Parker et al., 2001[27]	67 hospitalized adults, Australia	Age 18-65, English-speaking	Cognitive disturbance or cerebral pathology	New 16-item screening instrument (18)	Research psychiatrist	HADS or BDI-PC	Not specified	32.8%	100%	96%	—
Samaras et al., 2013[28]	272 patients at a geriatric ward of a university hospital, Switzerland	Age >65, with neuropsychology consultation for memory concerns	Severe dementia	HAD-D (8)	Neuropsychologist	DSM-IV	Psychiatrist	39.7%	50.9%	69.5%	AUC: 0.60
Koenig et al., 1992[29]	78 inpatients age ≥65 admitted for medical or neurological services in a VA hospital	Score of ≥15 on MMSE	Admitted to intensive care, severe medical illness, or communication problems	11-item interview (3)	Masters level social worker	Formal psychiatric structured interview	Psychiatrist	15%	83%	77%	Correlated with GDS (.92), Zung Depression Scale (.58) and CES-D (.67)

NOTE: Abbreviations: AUC, area under the curve (receiver-operator curve); BAS, Brief Assessment Schedule; BASDEC, Brief Assessment Schedule Depression Cards; BDI, Beck Depression Inventory; BDI-PC, Beck Depression Inventory, Primary Care version; BDI-SF, Beck Depression Inventory-Short Form; CES-D, Center for Epidemiological Studies-Depression; CIS-R, Clinical Interview Schedules, Revised; CVA, cerebrovascular accident; DIA-S, Depression in Old Age Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed; EPDS, Edinburgh Postnatal Depression Scale; GDS-4, Geriatric Depression Scale, 4-item version; GDS-5, Geriatric Depression Scale, 5-item version; GDS-15, Geriatric Depression Scale, 15-item version; GDS-30, Geriatric Depression Scale, full version; GMS, Geriatric Mental State Schedule; HAD-D, Hospital Anxiety and Depression Scale, Depression subscale; HADS, Hospital Anxiety and Depression Scale; MADRS, Montgomery-Åsberg Depression Scale; mDSS, Modified Depression Signs Scaled; MMSE, Mini-Mental State Examination; NPV, negative predictive value; NRS, Numeric Rating Scale; PHQ-2, Patient Health Questionnaire, 2-item version; PHQ-9, Patient Health Questionnaire, 9-item version; PPV, positive predictive value; PSE, Present State Examination; RRS, Retardation Rating Scale; SCL-5, Symptom Check List, 5-item version; SIDI, Stroke Inpatient Depression Inventory; STOP-D, Screening Tool for Psychological Distress.

TABLE 2. Clinical and Utilization Outcomes Among Inpatients Screened for Depression

Study	Study Design	Depression Screening Tool	Setting	Population	Sample Size	Prevalence of Depression	Clinical or Utilization Outcome	Summary of Findings
Albrecht et al., 2014[4]	Prospective cohort design	GDS-15	Academic medical center, United States	Adults age ≥60 on general medical and surgical services	750	19%	Unplanned readmission within 30 days	In multivariate logistic regression models, depressive symptoms were not associated with readmission
Cully et al., 2005[30]	Retrospective case-control	GDS-30	Inpatient rehabilitation unit, United States	Patients with and without stroke, mean age 76	Stroke: 207; No stroke: 302	31% using GDS (cutoff: ≥11)	Functional abilities, including self-care, body mobility, sphincter control at discharge	Depression was associated with worse self-care, body mobility, sphincter control, and communication/social interaction across both groups (ANCOVA, $P < 0.05$)
Mitchell et al., 2010[31]	Secondary analysis on randomized clinical trial	PHQ-9	Urban academic safety-net hospital, United States	Hospitalized adults, mean age 50, 52.1% black	738	32%	Hospital utilization within 30 days of discharge (emergency department and readmissions)	Hospital visits were greater for depressed patients (56 vs. 30 visits per 100 patients, adjusted for potential confounders, $P < 0.001$)
Huffman et al., 2011[32]	Prospective study of participants randomized into collaborative or usual care	PHQ-2, PHQ-9	Academic medical center, United States	Patients admitted for acute cardiac disease	175	Patients were included on basis of positive screen for depression	Adequate depression treatment at discharge, anxiety (measured by HADS), mental and physical HRQoL, and cardiac symptoms	Depression was associated with poor mental and physical health. Collaborative care subjects were more likely to receive adequate depression treatment by discharge
Pierlussi et al., 2012[33]	Secondary analysis of prospective cohort study	CES-D	Two urban teaching hospitals, United States	General hospitalized patients, age ≥70	1129	36.3%	IADLs, self-rated global health, mortality	At 1-year follow-up, patients with worse depressive symptoms at discharge maintained fewer independent IADLs and basic activities of daily living
Helvik et al., 2010[34]	Cross-sectional	HADS, MADRS, MMSE	Internal medicine service, rural hospital, Norway	Hospitalized adults age >65, mean age 80.7, 50% female	484	10%	Scale for self-maintaining activities of daily living and IADLs	Depression was associated with less independence in performing daily activities, a higher number of medications (not specified), and impaired reading vision
Unsar et al., 2010[35]	Cross-sectional	GDS	University hospital, Turkey	Hospitalized adults ≥60	100	64%	Length of illness, mobility, pain/discomfort, EQ-5D	Mobility, pain/discomfort, EQ-5D index and visual analog scale scores were significantly worse in the depressed elderly than in the nondepressed elderly

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without formal psychiatric training[15–23]; and 6 studies evaluated instruments administered by mental health professionals.[24–29] Four studies compared different instruments that were administered in the same manner (eg, both self-administered by patients).[12–14,22] In the remaining studies, both instruments and methods of administration differed between the index and reference conditions.

Eight studies tested brief instruments with 5 or fewer items, most of which exhibited good sensitivity (range 38%–91%) and specificity (range 68%–86%) relative to longer instruments.[12,14–19,22] In 2 of these studies, instruments were self-administered. In 1 case, a single self-administered item from the STOP-D instrument ("Over the past 2 weeks, how much have you been bothered by feeling sad, down, or uninterested in life?") performed nearly as well as the 14-item Hospital Anxiety and Depression Scale.[14] In the other 6 studies testing brief instruments, the instruments were administered by individuals without formal training.[15–19,22] In 1 such study, geriatricians asking 2 questions about depressed mood and anhedonia performed well compared with a formal psychiatric interview.[17]

Four studies tested variations of the Geriatric Depression Scale (GDS).[12,18,21,23] In 3 of these studies, abbreviated versions of the GDS exhibited relatively high sensitivity and specificity.[12,18,21] However, a study comparing the 15-item GDS (GDS-15) with the GDS-4 found that GDS-15 correctly classified 10% more patients with suspected depression.[12] Two studies examined variations of the Patient Health Questionnaire (PHQ). One study found that both the PHQ-2 and PHQ-9 obtained by staff nurses performed well relative to a comprehensive assessment by a trained advanced practice nurse.[13,19]

When reported, positive predictive value, negative predictive value, and area under the receiver-operator curve were generally high.

Depression and Clinical or Utilization Outcomes

Of the 12 studies that reported either clinical or utilization outcomes for depression screening in an inpatient set-

TABLE 2. Clinical and Utilization Outcomes Among Inpatients Screened for Depression *(continued)*

Study	Study Design	Depression Screening Tool	Setting	Population	Sample Size	Prevalence of Depression	Clinical or Utilization Outcome	Summary of Findings
Cullum et al., 2008[36]	Prospective cohort design	GDS-15	District general hospital, United Kingdom	Medical inpatients age ≥65	617	43.80%	Length of hospital stay, discharge to community hospital for rehabilitation, institutional care or usual place of residence, dying in the hospital	GDS score was associated with a greater risk of inpatient death, and of living in care home rather than usual residence. After adjusting for gender, depressive symptoms did not make a difference on length of hospital stay
McCusker et al., 2007[37]	Observational prospective study	DSM-IV Diagnostic Interview Schedule	Two university hospitals, Canada	Medical inpatients age ≥65, positive screen for depression	210	Patients were included on basis of positive screen for depression	SF-36	Depressed patients had lower SF-36 scores for both physical and mental health at 12-month follow-up than nondepressed patients (not included in the sample)
Cullum et al., 2003[38]	Prospective cohort design	GDS-15	Medical wards of district general hospital, United Kingdom	Consecutive medical inpatients age ≥65	61	59.02%	Length of hospitalization	Length of stay was significantly longer for patients who screened positive for depression (24 days) than patients who screened negative (13 days)
Beach et al., 2013[39]	Prospective cohort design	PHQ-9	Cardiac units of a hospital, United States	Patients admitted to the cardiac units for acute coronary syndrome, heart failure, or arrhythmia	172	Patients were included on basis of positive screen for depression	Cardiac readmission during 6-month follow-up	Patients with higher PHQ-9 scores were more likely to be readmitted within 6 months. Patients rehospitalized had a mean score of 18.5 (SD = 3.7); patients not rehospitalized had a mean score of 17.0 (SD = 3.3)
Williams et al., 2004[40]	Prospective cohort design	ICD-9	National cohort of patients discharged from any VA medical center with a primary diagnosis of ischemic stroke, United States	Ischemic stroke patients discharged between October 1, 1990, and September 30, 1997	51,119	5%	Mortality within 3 years of stroke	After controlling for specific cardiovascular and mortality risks using the Charlson Index, poststroke depression independently increased risk of death by 13%

Abbreviations: CES-D, Center for Epidemiological Studies-Depression; EQ-5D, European Quality of Life instrument-5 dimensions; GDS-15, Geriatric Depression Scale, 15-item version; GDS-30, Geriatric Depression Scale, full version; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; IADLS, Instrumental activities of daily living; ICD-9, International Classification of Diseases, Ninth Revision; MADRS, Montgomery-Åsberg Depression Scale; MMSE, Mini-Mental State Examination; PHQ-2, Patient Health Questionnaire, 2-item version; PHQ-9, Patient Health Questionnaire, 9-item version; SF-36, Short Form Health Survey; VA, Veterans Administration.

ting,[4,30–40] 3 measured rates of rehospitalization.[4,31,39] The other 9 studies tested for associations between symptoms of depression and either health or treatment outcomes. Table 2 provides a more detailed description of the study designs and results.

Other studies found that depression was associated with reduced functional abilities such as mobility and self-care,[30,32–34] and increased hospital readmission[31] as well as physical and mental health deficits.[37] Interestingly, although 1 study did not find that depression and hospital readmission were closely linked (frequency at 19%), it found that comorbid illness and previous hospitalizations predicted readmission.[4]

We also evaluated the associations between depression diagnosed in the inpatient studies and 2 types of outcomes. The first type includes clinical outcomes including symptom severity, quality of life, and daily functioning. Most studies we identified assessed clinical outcomes, and all detected an association between depression and worse clinical outcomes. The second type includes healthcare utilization, which can be measured with the patients' length of hospital stay, readmission and cost of care. In 1 such study, Mitchell aet al.[31] reported a 54% increase in readmission within 30 days of discharge among patients who screened positive for depression.[31] Additionally, Cully et al.[30] found that depression may impinge on the recovery process of acute rehabilitation patients.

DISCUSSION

The purpose of this study was to describe the feasibility and performance of depression screening tools in inpatient medical settings, as well as associations between depression diagnosed in the inpatient setting and clinical and utilization outcomes. The median rate at which depression was detected among inpatients was 33%, ranging from 5% to 60%. Studies from several individual hospitals indicated that depression can be associated with higher healthcare utilization, including return to the hospital after discharge, as well as worse clinical outcomes. To detect undiagnosed depression among inpatients, screening appears feasible. Depression screening instruments generally exhibited good sensitivity and specificity relative to comprehensive clini-

cal evaluations by mental health professionals. Furthermore, several self-administered and brief instruments had good performance. Prior authors have reported that screening for depression among inpatients may not be particularly burdensome to patients or staff members.[41]

The studies we reviewed used diverse screening instruments. Further research is needed to determine which tools are preferable in which patient populations, and to confirm that brief instruments are adequate for screening. The GDS is widely used, and many patients hospitalized in the United States fall into the geriatric group. The PHQ has been validated for self-administration and is widely used among outpatients[42]; it may be more suitable for younger populations. We found that several abbreviated versions of these and other screening instruments have exhibited good sensitivity and specificity among inpatients. However, many of the studies excluded patients with cognitive impairment or communication barriers. For individuals with auditory impairment, the Brief Assessment Schedule Depression Cards (BASDEC) might be an option. Used in 2 studies, the BASDEC involves showing patients a deck of 19 easy-to-read cards. The time required to administer the BASDEC is modest.[15,23] Sets of smiley face diagrams might also be suitable for some patients with communication barriers or cognitive impairment. An ineligible study among stroke survivors found that selecting a sad face had a sensitivity of 76% and specificity of 77% relative to a formal diagnostic evaluation for depression.[43]

In considering the instruments that may be most suitable for inpatients, the role of somatic symptoms is also important because these can overlap between depression and the medical conditions that lead to hospitalization.[44–46] Prior investigators found, for example, that 47% of Beck Depression Inventory (BDI) scores were attributable to somatic symptoms among patients hospitalized after myocardial infarction, whereas 37% of BDI scores were attributable to somatic symptoms among depressed outpatients.[47] Future research is needed to determine the significance of somatic symptoms among inpatients, including whether they should be considered during screening, add prognostic value, or warrant specific treatment. In addition, although positive and negative predictive values were generally high among the screening instruments we evaluated, confirming the diagnosis of depression with a thorough clinical assessment is likely to be necessary.[44,45]

Despite the high prevalence of depression, associations with suboptimal outcomes, and the good performance of screening tools to date, screening for depression in the inpatient setting has received little attention. Prior authors have questioned whether hospital-based screening is an efficient and effective way to detect depression, and have raised valid concerns regarding false-positive diagnoses and unnecessary treatment, as well as a lack of randomized controlled trials.[7,48,49] Whereas some studies suggest that depression is associated with greater healthcare utilization,[3,4] little information exists regarding whether screening during hospitalization and treating previously undiagnosed depression improves clinical outcomes or reduces healthcare utilization.

Several important questions remain. What is the pathophysiology of depressed mood during hospitalization? How often does depressed mood during hospitalization reflect longstanding undiagnosed depression, longstanding undertreated depression, an acute stress disorder, or a normal if unpleasant short-term reaction to the stress of acute illnesses? Do the manifestations and effects of depressed mood differ among these situations? What is the prognosis of depressed mood occurring during hospitalization, and how many patients continue to have depression after recovery from acute illness; what factors affect prognosis? In a small sample of hospitalized patients, nearly 50% of those who had been depressed at intake remained depressed 1 month after discharge.[50] Given that most antidepressant medications have to be taken for several weeks before effects can be detected, what, if any, approach to treatment should be taken? More research is needed on the effectiveness and cost-effectiveness of diagnosing and treating depression in the inpatient setting.

This work has several limitations. We found relatively few studies meeting eligibility criteria, particularly studies assessing clinical and utilization outcomes among depressed inpatients. Among the screening tools that were studied in the hospital setting, the highly diverse instruments and modes of administration precluded a quantitative synthesis such as meta-analysis. Prior meta-analyses on specific screening tools have focused on outpatient populations.[51–53] Furthermore, we did not evaluate study quality or risk of bias.

In conclusion, screening for depression in the inpatient setting via patient self-assessment or assessment by hospital staff appears feasible. Several brief screening tools are available that have good sensitivity and specificity relative to diagnoses made by mental health professionals. Limited evidence suggests that screening tools for depression may be ready to integrate into inpatient care.[41] Yet, although depression appears to be common and associated with worse clinical outcomes and higher healthcare utilization, more research is needed on the benefits, risks, and potential costs of adding depression screening in the inpatient healthcare setting.

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Acute Kidney Injury Is Important in the Hospital and Afterward

Benjamin J. Lee, MD[1*], Chi-yuan Hsu, MD, MSc[1]

[1]*Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, California.*

Acute kidney injury (AKI) is a major contributor to morbidity and mortality in hospitalized patients across the world.[1] Affecting up to 20% of all admissions (depending on which definition of AKI is used),[2] AKI is the most common reason for new-inpatient nephrology consultation. Recent data suggest that AKI incidence has risen rapidly, by up to 10% per year.[3,4]

AKI is associated with a variety of serious short- and long-term complications. Approximately 33% to 60% of critically ill patients who develop dialysis-requiring AKI do not survive to hospital discharge, and mortality associated with dialysis-requiring AKI is greater than that associated with other serious conditions such as myocardial infarction or acute respiratory distress syndrome.[5] Even relatively mild AKI in the acute inpatient setting appears to be an independent risk factor for mortality.[6]

For several decades, many physicians believed that AKI was a self-limited process followed by complete recovery of renal function to pre-AKI levels among survivors. (Numerous trainees have been taught some variant of the old adage: "If the patients survive, so will their kidneys.") But studies linking AKI with the development of new-onset chronic kidney disease (CKD) or the accelerated progression of pre-existing CKD have changed this view.[7] One important reason the long-term impact of AKI hasn't been appreciated is that, traditionally, clinical studies of AKI examined in-hospital outcomes such as short-term mortality and resource usage and did not consider what transpired months to years after discharge. More recently, epidemiologic studies linking inpatient events with outpatient outcomes have filled this knowledge gap.[8] Contemporary animal models of AKI have shed light on potential mechanisms of maladaptive repair after AKI, characterized by fibrosis, vascular rarefaction, tubular loss, glomerulosclerosis, and chronic interstitial inflammation, all of which result in renal function decline. So over the last decade there has been a paradigm shift in how we think about AKI and CKD. Rather than distinct entities, AKI and CKD are now viewed as interconnected syndromes since AKI is a risk factor for CKD progression and CKD is a risk factor for new episodes of AKI.[9]

Two studies published in this issue of the *Journal of Hospital Medicine* augment our understanding of AKI and its clinical impact in hospitalized patients. Analyzing data from the National Inpatient Sample, Silver et al.[10] found that hospitalizations that include AKI are substantially costlier and associated with longer lengths of stay than hospitalizations without AKI. The authors also highlight that the additional economic costs of AKI exceeded those of many other higher-profile yet less-common acute medical conditions, such as myocardial infarction and gastrointestinal bleeding. These results re-emphasize the important economic burden of AKI at a national level and expand on prior literature by confirming findings previously limited to single-center and regional studies. Better defining the impact AKI has on our healthcare system could help ensure that adequate resources are invested to combat AKI.

The second study, by Rutter et al.,[11] found that among hospitalized patients with normal baseline renal function, use of vancomycin in combination with piperacillin-tazobactam is associated with a higher incidence of AKI after antibiotic exposure than use of either agent as monotherapy. This association persisted even after adjusting for potential confounders such as underlying comorbidities, exposure to nephrotoxic agents, documented hypotension, and baseline renal impairment. This study adds to a growing body of literature that suggests synergistic nephrotoxicity between vancomycin and piperacillin-tazobactam. It underscores that any medical intervention—even treatments typically envisioned as non-hazardous and frequently life-saving—involve inherent risks and should prompt the medical community to promote proper antimicrobial stewardship. Whether such exposures to vancomycin or beta-lactam derivatives cause AKI via direct tubular damage, interstitial nephritis, or some other novel mechanism remains to be elucidated. Better delineation of the contemporary causes of AKI, including increased antibiotic exposure, is the first step toward identifying ways to reduce AKI incidence.

Both of these papers serve to highlight the clinical importance of AKI among hospitalized patients. Their findings re-emphasize the need for vigilance in detecting AKI and intervening early to achieve the best clinical outcomes.

Given recent understanding that survivors of AKI are at greater risk for more rapid loss of renal function long after hospital discharge, one goal the US Department of Health and Human Services put forth for Healthy People 2020 is to "increase the proportion of hospital patients who incurred AKI who have follow-up renal evaluation in 6 months post-discharge" (10% improvement targeted).[12] Transitions of care after hospitalizations complicated by AKI require special attention to ensure that patients' needs are optimally

***Address for correspondence and reprint requests:** Benjamin J. Lee, MD, Division of Nephrology, University of California San Francisco, 533 Parnassus Avenue, U404, San Francisco, CA 94143; Telephone: 415-476-1812; Fax: 415-476-3381; E-mail: bjlee@ucsf.edu

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monitored and managed during the critical post-discharge period. One recent study analyzing discharge documentation for hospitalizations including AKI found that fewer than half of the discharge summaries and patient instructions commented on the presence, cause, or course of AKI, indicating clear room for improvement.[13] And currently, it appears that only a minority of patients with AKI—even AKI severe enough to require dialysis—are seen by a nephrologist within 90 days of discharge.[14]

Hospitalists play a crucial role in coordinating care as vulnerable patients transition from the inpatient to outpatient setting. We suggest that AKI should be properly documented in the discharge summary. In addition, patients should be informed that they experienced AKI so they can discuss with future caregivers potential strategies to avoid additional renal insults. Discharge referrals to nephrology should be arranged for high-risk patients, including those whose renal function remains decreased at discharge or those who had recurrent AKI episodes during prior hospitalizations. For patients with pre-hospitalization baseline CKD, nephrology should be consulted before indefinitely discontinuing medications like angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These medications are indispensable in retarding the progression of proteinuric CKD, even though they may predispose patients to AKI under certain circumstances (eg, in states of decreased renal perfusion). Adopting these simple steps may substantially improve the long-term outcomes of patients who experience AKI during hospitalization.

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