Anemia is associated with poor quality of life and increased risk for death and hospitalization in population-based and cohort investigations.1-7 Evidence suggests that patients with normal hemoglobin (Hgb) values on hospital admission who subsequently develop hospital-acquired anemia (HAA) have increased morbidity and mortality compared to those who do not.8,9 HAA is multifaceted and may occur as a result of processes of care during hospitalization, such as hemodilution from intravenous fluid administration, procedural blood loss and phlebotomy, and impaired erythropoiesis associated with critical illness.8,9 Moreover, correcting anemia by red blood cell transfusion also carries risk.10-13

Our primary objective was to examine the prevalence of HAA in a population of medical and surgical patients admitted to a large quaternary referral health system. Our secondary objectives were to examine whether HAA is associated with increased mortality, length of stay (LOS), and total hospital charges compared to patients without HAA.

METHODS

Patient Population and Data Sources

The patient population consisted of 417,301 hospitalizations in adult patients (≥18 years of age) who were admitted to the Cleveland Clinic Health System from January 2009 to September 2011. Data for these hospitalizations came from 2 sources. Patient demographics, baseline comorbidities, and outcomes were extracted from the University HealthSystem Consortium’s (UHC) clinical database/resource manager. UHC is an alliance of 116 US academic medical centers and their 272 affiliated hospitals, representing more than 90% of the nation’s nonprofit academic medical centers. These data had originally been retrieved from our hospitals’ administrative data systems, normalized according to UHC standardized data specifications.
Anemia
The World Health Organization (WHO) defines anemia as a Hgb value $<12$ g/dL in women and $<13$ g/dL in men. HAA was defined as a nadir Hgb value during the course of hospitalization meeting WHO criteria. We further grouped Hgb by degree into no anemia, mild anemia ($Hgb >11$ and $<12$ g/dL in women, $>11$ and $<13$ g/dL in men), moderate anemia ($Hgb >9$ and $<11$ g/dL), and severe anemia ($Hgb \leq 9$ g/dL).

Outcomes
Outcomes were all-cause in-hospital mortality, total hospital LOS, and total hospital charges.

Data Analysis
For risk adjustment, we used methods developed by Elixhauser and colleagues\textsuperscript{14} for use with in-patient administrative databases. These included a comprehensive set of comorbidity indicators, used to control for patients’ underlying conditions in models of...
Our primary analysis excluded patients with anemia at the time of hospitalization based on administratively determined POA anemia positive indicator coding. We also performed a sensitivity analysis to exclude patients with anemia based on the first Hgb values determined by laboratory testing.

All analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC) and R version 2.13 (www.r-project.org).

## RESULTS
### Prevalence of HAA
Among the 188,447 hospitalizations, 139,807 patients (74%) developed HAA and 48,640 (26%) did not. Of the 74%, 40,828 developed mild, 57,184 moderate, and 41,795 severe HAA (Figure 2). Patients who developed HAA were older than those who did not and had more comorbidities, including hypertension, heart failure, peripheral arterial disease, and renal and liver disease. They were hospitalized more commonly for surgical intervention than were those who did not develop HAA (Table 1). Time-related patterns for developing HAA, however, showed that it developed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Anemia, n = 48,640</th>
<th>Mild, n = 40,828</th>
<th>Moderate, n = 57,184</th>
<th>Severe, n = 41,795</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission, y</td>
<td>55 ± 18</td>
<td>58 ± 18</td>
<td>58 ± 19</td>
<td>61 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>25,123 (52)</td>
<td>17,938 (44)</td>
<td>30,650 (63)</td>
<td>23,533 (58)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39,100 (80)</td>
<td>32,610 (80)</td>
<td>45,977 (80)</td>
<td>33,810 (81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>7590 (16)</td>
<td>6607 (16)</td>
<td>6946 (16)</td>
<td>6204 (16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>1960 (4.0)</td>
<td>1611 (3.9)</td>
<td>2261 (4.0)</td>
<td>1781 (4.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospitalization type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Surgery</td>
<td>9681 (20)</td>
<td>14,076 (34)</td>
<td>26,100 (46)</td>
<td>27,865 (67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medicine</td>
<td>38,958 (80)</td>
<td>26,750 (66)</td>
<td>31,081 (54)</td>
<td>13,922 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25,591 (53)</td>
<td>22,218 (54)</td>
<td>29,963 (52)</td>
<td>24,257 (59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2811 (5.8)</td>
<td>3182 (7.8)</td>
<td>5086 (9.3)</td>
<td>4278 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1201 (2.5)</td>
<td>1259 (3.1)</td>
<td>2126 (3.7)</td>
<td>1890 (4.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary circulation disease</td>
<td>667 (1.4)</td>
<td>730 (1.8)</td>
<td>1221 (2.1)</td>
<td>1484 (3.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2417 (5.0)</td>
<td>2728 (6.7)</td>
<td>4817 (7.3)</td>
<td>4508 (11)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Renal failure</td>
<td>1096 (2.3)</td>
<td>1402 (3.4)</td>
<td>2517 (4.4)</td>
<td>6214 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rheumatoid arthritis/collagen vascular disease</td>
<td>1250 (2.6)</td>
<td>1260 (3.1)</td>
<td>2214 (3.9)</td>
<td>1729 (4.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Solid tumor without metastasis</td>
<td>499 (1.0)</td>
<td>760 (1.9)</td>
<td>1297 (2.3)</td>
<td>1123 (2.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Metastatic cancer</td>
<td>489 (1.0)</td>
<td>789 (1.9)</td>
<td>1889 (3.3)</td>
<td>1993 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>499 (1.0)</td>
<td>789 (1.9)</td>
<td>1889 (3.3)</td>
<td>1993 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute liver disease</td>
<td>1250 (2.6)</td>
<td>1260 (3.1)</td>
<td>2214 (3.9)</td>
<td>1729 (4.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1008 (2.3)</td>
<td>1402 (3.4)</td>
<td>2517 (4.4)</td>
<td>6214 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute pericarditis</td>
<td>7494 (15)</td>
<td>5177 (13)</td>
<td>7112 (12)</td>
<td>5279 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>972 (2.0)</td>
<td>1240 (3.0)</td>
<td>2746 (4.9)</td>
<td>5641 (14)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Acute kidney injury</td>
<td>7262 (15)</td>
<td>7501 (18)</td>
<td>12,829 (22)</td>
<td>17,201 (41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>2345 (5.7)</td>
<td>2544 (4.4)</td>
<td>1727 (4.1)</td>
<td>657 (1.6)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Acute respiratory failure</td>
<td>5999 (12)</td>
<td>4662 (11)</td>
<td>6605 (12)</td>
<td>4885 (12)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as mean (standard deviation) or n (%).
earlier in men and more frequently with medical versus surgical hospitalization (Figure 3).

Hospital Mortality and HAA
Unadjusted mortality progressively increased with increasing degree of HAA: no HAA, 0.78% (n = 378); mild HAA, 0.99% (n = 405); moderate HAA, 1.5% (n = 881); and severe HAA, 4.6% (n = 1936) (P < 0.001) (Figure 4A). Patients with mild HAA did not have higher risk-adjusted mortality than those not having HAA (odds ratio: 1.02, 95% confidence interval [CI]: 0.88-1.17). However, as HAA increased to moderate and severe, risk of hospital mortality increased in a dose-dependent manner compared with patients not developing HAA: moderate HAA, 1.51 (95% CI: 1.33-1.71, P < 0.001) and severe HAA, 3.28 (95% CI: 2.90-3.72, P < 0.001) (Figure 5A) (see Supporting Information, Supplement A, in the online version of this article).

Resource Utilization and HAA
Length of Hospital Stay
Unadjusted median (25th, 75th percentiles) LOS was progressively higher in patients who developed HAA: no HAA, 3 days (2, 4); mild HAA, 3 days (2, 5); moderate HAA, 4 days (2, 6); and severe HAA, 7 days (4, 12) (P < 0.001) (Figure 4B). Mild HAA was associated with a mean relative increase of 1.09 (95% CI: 1.08-1.10, P < 0.001); moderate HAA, 1.28 (95% CI: 1.26-1.29, P < 0.001); and severe HAA, 1.88 (95% CI: 1.86-1.89, P < 0.001). For example, if expected LOS was 4 days for a patient with no HAA, then for a patient with severe anemia, it would be 7.52 (a 1.88-fold increase) when all comorbidities were the same (Figure 5B) (see Supporting Information, Supplement A, in the online version of this article).

Total Hospital Charges
Unadjusted hospital charges became progressively higher as degree of HAA increased (P < 0.001) (Figure 4C). The mean relative increase was 1.06 (95% CI: 1.06-1.07, P < 0.001) for mild HAA compared with no HAA, 1.18 (95% CI: 1.17-1.19, P < 0.001) for moderate HAA, and 1.80 (95% CI: 1.79-1.82, P < 0.001) for severe HAA. For example, if the expected total charge was $30,000 for a patient with no HAA, then for a patient with severe anemia, it would be $54,000 (a 1.80-fold increase) when all comorbidities were the same (Figure 5C) (see Supporting Information, Supplement A, in the online version of this article).

Sensitivity Analysis
Among patients without anemia based on the first available Hgb value (n = 96,975), 50% of patients developed HAA: mild HAA, 24% (n = 23,063); moderate HAA, 19% (n = 18,134); and severe HAA, 8% (n = 7373). There was a similar relationship between increasing magnitude of HAA and an increase in mortality, LOS, and total charges in the unadjusted and adjusted analyses (see Supporting Information, Supplement C, in the online version of this article).

DISCUSSION
A substantial number of patients entering our health system became anemic during the course of their hospitalization. Among those who developed HAA, in-hospital mortality was higher, LOS longer, and total hospital charges greater in a dose-dependent manner. A recent editorial noted that HAA might be a hazard of hospitalization similar to other complications, such as infections and deep vein thrombosis. Others have noted negative consequences of HAA in subpopulations of hospital patients. Salisbury and colleagues examined 17,676 patients with acute myocardial infarction who had normal Hgb on admission. They defined HAA as development of new anemia during hospitalization based on nadir Hgb. HAA developed in 57.5% of patients and was associated with increased mortality in a progressive manner. Risk-adjusted odds ratios for in-hospital death were greater in patients with moderate and severe HAA, 1.38 (95% CI: 1.10-1.73) and 3.39 (95% CI: 2.59-4.44), respectively. A separate investigation of 2902 patients from a multicenter registry...
of patients admitted to the hospital with acute myocardial infarction reported that nearly half of those with normal Hgb values on admission developed HAA. Most of these patients did not have documented bleeding; therefore, the authors suggested that HAA was not a surrogate for bleeding during hospitalization. Moreover, HAA was associated with higher mortality and worse health status 1 year after myocardial infarction. Others have reported that development of HAA is not uncommon in the setting of acute myocardial infarction and is associated with increased long-term mortality.

Development of anemia during hospitalization is multifactorial and may result from procedural bleeding, phlebotomy, occult bleeding, hemodilution from intravenous fluid administration, and blunted erythropoietin production associated with critical illness. An investigation of general internal medicine patients reported phlebotomy was highly associated with changes in Hgb levels and contributed to anemia during hospitalization. The authors reported that for every 1 mL of blood drawn, mean decreases in Hgb and hematocrit were $0.07 \pm 0.011$ g/L and $0.019 \pm 0.003\%$, respectively. They suggested reporting cumulative phlebotomy volumes to physicians and use of pediatric-sized tubes for collection. Salisbury and colleagues reported that mean phlebotomy volume was higher in patients who developed HAA; for every 50 mL of blood drawn, the risk of moderate to severe HAA increased by 18%. In an intensive care population, Chant and colleagues reported small decreases in phlebotomy volume were associated with reduced transfusion requirements in patients with prolonged stay.

Attempts to ameliorate HAA should focus on modifiable processes-of-care factors. Patients with chronic illness have blunted erythropoiesis and therefore cannot mount an adequate response to blood loss from procedures or phlebotomy. Whether use of erythropoietin, iron, or both would be effective in this population requires further investigation. One of the most studied risk factors for HAA is blood loss from hospital laboratory testing. Sanchez-Giron and Alvarez-Mora found that all laboratory tests could be performed with smaller-volume collection tubes without need for additional samples. Others have
proposed batching laboratory requests, recording cumulative daily blood loss due to phlebotomy for individual patients, and use of blood conservation devices in intensive care units.

Figure 3 suggests that surgical patients develop anemia slightly later than medical patients. Features specific to surgery, such as perioperative intravenous fluid loading, “third spacing,” and subsequent plasma volume expansion when reabsorption occurs days later, likely contribute to differences in trends for development of HAA. In addition, specific surgical cases with highly anticipated red blood cell loss should make use of antifibrinolytic agents to reduce blood loss and red cell salvage devices to reprocess and infuse shed blood.

**Limitations**

A recent commentary explored the question of benchmarks for anemia diagnosis, and in particular, what defines the lower limit of normal. Although we used WHO criteria, others have used criteria establishing lower benchmarks according to race and gender. Our results would have been similar if we had used these lower benchmarks, because our moderate and severe anemia Hgb cutoff values were beneath alternative benchmarks for diagnosing anemia. For example, Beutler and Waalen provide a definition of anemia that includes an Hgb cutoff of 12.2 g/dL for white women aged 20 to 49 years, 11.5 g/dL for black women of similar age, 13.7 g/dL for white men, and 12.9 g/dL for black men.

Our study is limited by the nature of administrative data. However, use of demographic data, hospitalization type, and use of a large number of comorbidities for risk adjustment improved our findings. Adding nonadministrative clinical laboratory data from the electronic record for patient Hgb values provided us with a more accurate diagnosis of HAA and an ability to further subdivide anemia into mild, moderate, and severe categories that have prognostic implications. We are aware of the inherent limitations associated with use of administrative data. However, coded data are currently readily available and are the source of information on which many healthcare policies are made.

The POA anemia administrative code was used to identify patients with preexisting anemia. We did not use the first Hgb value upon admission because it is often made following interventions (eg, surgical patients have preoperative laboratory testing prior to admission, and the first Hgb value available following hospitalization is commonly obtained following surgical interventions). However, we performed a sensitivity analysis that defined preexisting anemia based on the first available Hgb value. The results from the sensitivity analysis were consistent with our primary findings with the use of administrative data coding. Of note, use of administrative codes for determining POA indicators is consistent with methods employed
for all current publically reported quality and patient safety initiatives. Specifically, the Agency for Healthcare Research and Quality Patient Safety Indicators used by the Centers for Medicare and Medicaid Services to assess hospital quality of care and to modify reimbursement for services.

Our focus was on development of HAA; treatment of HAA with red blood cell transfusion and standardized blood draw orders were not investigated. Finally, our results are reflective of a single health system; further work with multicenter data would help clarify our findings.

CONCLUSION
Development of HAA is common and has important healthcare implications, including higher in-hospital mortality and increased resource utilization. Treating HAA by transfusion has attendant morbidity risks and increased costs. Hospitals must continue to focus on improving patient safety and raising awareness of HAA and other modifiable hospital-acquired conditions. Closer prospective investigation for both medical and surgical patients of cumulative blood loss from laboratory testing, procedural blood loss, and a risk-benefit analysis of treatment options is necessary.

Disclosure: Nothing to report.

References