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To the editor:

Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukemia: a matched cohort study

In recent years, there has been growing evidence that hospital volume affects survival among patients undergoing a variety of surgical procedures and medical treatments.[1,2] Whether case volume affects outcomes after chemotherapy among patients with acute myeloid leukemia (AML) remains unknown. Several complications may occur during AML chemotherapy including infections, leukostasis, intracranial hemorrhage, and other bleeding complications, and management of these conditions requires specialized experienced health professionals and resources. Hospitals with higher volumes may be more adept at managing these complications and hence have a lower mortality rates.

We used the Nationwide Inpatient Sample (NIS) database from the years 2009 to 2011 to explore this hypothesis.[3] NIS is the largest all-payer inpatient database available in the United States and is sponsored by the Agency for Healthcare Research and Quality. We identified the study cohort using code V58.11 (Encounter for antineoplastic therapy) as the principle diagnosis and using the International Classifications of Diseases, 9th revision (ICD-9-CM) code 205 for AML as a secondary diagnosis.[4] Hospitals were divided into quartiles (25th, 50th, and 75th), based on the annual number of cases of AML admitted for chemotherapy. Subsequently, they were divided into high-volume centers (>75th percentile) and low-volume centers (<75th percentile) based on a review of similar studies.[5,6] We used propensity matching with a nearest neighbor-matching algorithm to build a matched dataset for high-volume centers and low-volume centers controlling for covariates affecting outcomes including age, sex, comorbidity (using the Charlson Comorbidity Index), insurance status, income status (in quartiles), hospital size, location, ownership, and day of admissions (weekend vs weekday). Parametric methods for independent samples were used for analyzing the propensity-matched data set as suggested by Schafer and Kang in 2008.[7] Statistical analysis was done using STATA 13.0 (College Station, TX).

An estimated 15 446 hospitalizations were identified during the study period. After propensity matching, 3640 hospitalizations were selected for final analysis. This included 1150 (31%) cases in high-volume centers and 2489 (69%) cases in low-volume centers. The mortality rate was significantly higher in the low-volume (4.97%) vs the high-volume centers (1.59%) (odds ratio, 3.26; 95% confidence interval, 1.98-5.38; $P < .001$). After removing the elective cases from this cohort, the difference continued to remain significant (3.4% vs 0%, respectively; $P < .001$). The mean length of stay was similar between the low-volume centers and high-volume centers (14.6 vs 14.2 days; $P = .88$). Similarly, the mean cost of hospital stay was similar between the 2 groups ($101 945 vs $102 643; $P = .96$) (Table 1).

Our study demonstrates clear differences in mortality among patients undergoing chemotherapy for AML based on hospital volume. The most striking example for this "volume-outcome relationship" has been seen in certain cancer surgeries like esophagectomy, pancreatectomy, etc., which is possibly a reflection of "practice makes a man perfect."[8,9] However, the same relationship has also been shown to be true for medical conditions such as heart failure, pneumonia, and

Table 1. In-hospital outcomes of high-volume vs low-volume centers in a matched cohort of patients with acute myeloid leukemia admitted for chemotherapy

Category	High-volume center	Low-volume center	*P*
Mortality	1.59%	4.07%	<.001
Mean length of stay (SD)	14.22 (1.04)	14.59 (2.31)	.88
Costs of hospitalization	102653 (11242)	101945 (12585)	.96

SD, standard deviation.
P values calculated from χ^2 tests and analysis of variance.

sepsis.[10,11] These effects are possibly a result of increased provider experience, improved adherence to standard guidelines, adequacy of supportive staff and ancillary services, and greater financial capacity and resources.[10,11] In the context of cancer chemotherapy, higher-volume hospitals may have more experienced house staff capable of recognizing and managing chemotherapy complications at an earlier stage, leading to fewer deaths.

It is notable that the overall inpatient mortality among patients undergoing chemotherapy for AML was quite low compared with an early mortality rate of 12.2% reported by the Southwest Oncology Group.[12] This can be attributed to our inability to distinguish induction vs consolidation chemotherapy among the study cohort. Consolidation therapy involves the use of fewer and less-toxic chemotherapies and is associated with fewer complications and mortality.

Our study has several limitations. We were unable to separately analyze the impact of hospital volume on induction vs consolidation chemotherapy. Second, we were unable to analyze factors affecting prognosis such as cytogenetic and molecular profile, type of chemotherapy, performance scores, and use of supportive therapy such as growth factors. However, our study, being the first of its kind, generates a hypothesis that the volume-outcome relationship may hold true for chemotherapy for AML as well and should be explored in future studies.

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To the editor:

Insights from response to tyrosine kinase inhibitor therapy in a rare myeloproliferative neoplasm with *CALR* mutation and *BCR-ABL1*

Calreticulin (*CALR*) mutations have been reported primarily in the context of *JAK2* and *MPL* wild-type essential thrombocythemia and primary myelofibrosis.[1-5] *CALR* mutations are exceedingly rare in the setting of t(9;22)/*BCR-ABL1*,[4,5] with only a single report in the literature describing a case of an atypical myeloproliferative neoplasm (MPN) in which *CALR* mutation preceded *BCR/ABL1* fusion.[6]

Here, we describe a patient with *CALR* mutation seen in the context of an MPN with the Philadelphia chromosome. The patient was a 67-year-old man found to be hypertensive on routine physical examination. His workup revealed an elevated white blood cell (WBC) count of 25×10^9/L (normal, 4×10^9/L) that prompted bone marrow (BM) aspiration and a biopsy at the referring institution, which was interpreted as suggestive of the patient having an MPN. Conventional cytogenetics and real-time reverse transcriptase polymerase chain reaction (RT-PCR) performed at the referring institution were positive for t(9;22) and *BCR-ABL1* fusion, respectively. The patient was treated with dasatinib as frontline therapy and was referred to our institution for further evaluation and management. A complete blood count revealed a WBC count of 39.9×10^9/L (Figure 1A), hemoglobin of 14.1 g/dL,