Remnant Blood Quantification: *Informing the Definition of Minimal Risk in Clinical Research*

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ABSTRACT Guidelines from the Office for Human Research Protections regarding categories of research that institutional review boards (IRBs) may review through expedited procedures limit the volume of blood that can be obtained from research participants for minimal risk research purposes. As defined by the Common Rule, minimal risk research is research in which the probability and magnitude of harm or discomfort anticipated are not greater than the probability and magnitude of harm or discomfort encountered from routine clinical tests. For this study, we considered the volume of remnant blood following routine clinical tests in light of the current definition of minimal risk in research. Conducted at a single institution, this was a prospective cross-sectional study that evaluated blood draws from 122 patients. The median daily remnant blood volume was 11.6 (interquartile range [IQR]: 12.3, 15.2) ml for all patients and 12.9 (IQR: 13.1, 16.9) ml for patients admitted to the intensive care unit. Our findings regarding daily remnant blood volume suggest that the currently allowable blood-volume limits to qualify for expedited review or to qualify as not more than minimal risk research involving blood draws from nonhealthy adults are less than what patients experience in routine medical testing. These findings support permitting an increase in the allowable blood-volume limits to meet the regulatory definition of minimal risk research for obtaining expedited IRB review of studies in which blood samples will be collected.

KEYWORDS human subjects research, clinical research, remnant blood volume, institutional review board, minimal risk determination, expedited review

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Diagnostic testing is a fundamental component of the workup of patients in the emergency department and inpatient settings. The number of ordered and unordered laboratory tests and the volume of blood drawn appear to be increasing.[1] While diagnostic testing is essential for the complete evaluation of a patient, routine diagnostic testing is not without risk. Moreover, studies show that, in the clinical setting, more blood is drawn from patients than is actually needed to conduct diagnostic testing. For example, Dale et al. show that institutions discard a median volume of 2.8 ml for every complete blood count ordered.[2]

In the research context, the Office for Human Research Protections (OHRP) has issued guidelines regarding the volume of blood draws (over a certain period) that meet the regulatory definition of not more than minimal risk research for the purposes of an institutional review board (IRB) reviewing a research protocol under the Common Rule's expedited review provision. For nonhealthy adults and children, the OHRP guidelines state that for not more than minimal risk research, the amounts drawn may not exceed the lesser of 50 ml or 3 ml/kg in an eight-week period (with no more than two collections per week).[3] The frequency and quantity of blood draws affect risk determinations by IRBs, which may impact trial design and the feasibility of carrying out a study that includes the collection of blood from participants.

We used remnant blood volume, the blood volume remaining following all clinical laboratory testing, to quantify the magnitude of harm from routine laboratory testing. Previous studies to quantify remnant blood volume have been imprecise and based on surveys, blood tubes recorded in the hospital chart, or the volume requested by the laboratory.[4] Determining the remnant blood volume in routine laboratory testing would be a significant step toward further defining the minimal risk threshold for obtaining expedited IRB review of research protocols that involve blood draws.

STUDY METHODS

Our study was a prospective observational study to quantify the remnant volume of blood following laboratory evaluation of patients in the emergency department and inpatient setting at an academic medical center. The study was determined not to be human subjects research by the institution's IRB.

We planned to include patient information from the electronic medical records of 125 patients from whom blood was collected: 25 trauma-floor patients, 25 trauma-intensive care unit (ICU) patients, 25 medical-floor patients, 25 medical-ICU patients, and 25 patients discharged from the emergency department. (See appendix A for patient-inclusion criteria; the appendices can be found online, as explained in the "Supporting Information" section below.) We identified patient records through the trauma-team census, emergency department census, the medical-ICU census, and the general medical-team census at the University of Cincinnati Medical Center from October 2019 to December 2019. Research associates (Constand and Cabrera) collected the information. Source documentation was maintained in a secure data storage program and was used only for gathering blood tubes from the clinical laboratory. Remnant blood volume was determined as described in appendix B. Study data were collected and managed using REDCap electronic data capture tools hosted at The University of Cincinnati and Cincinnati Children's Hospital Medical Center.[5] Blood tubes were weighed for the entirety of each patient's hospitalization. The patient group did not change if the patient's level of care changed throughout hospitalization; the patient remained in the original disposition-based group (so called because "disposition" is used in describing a patient's destination following assessment and treatment in the emergency department). Measurements were completed until the patient was discharged from the facility or the end of the study, whichever came first.

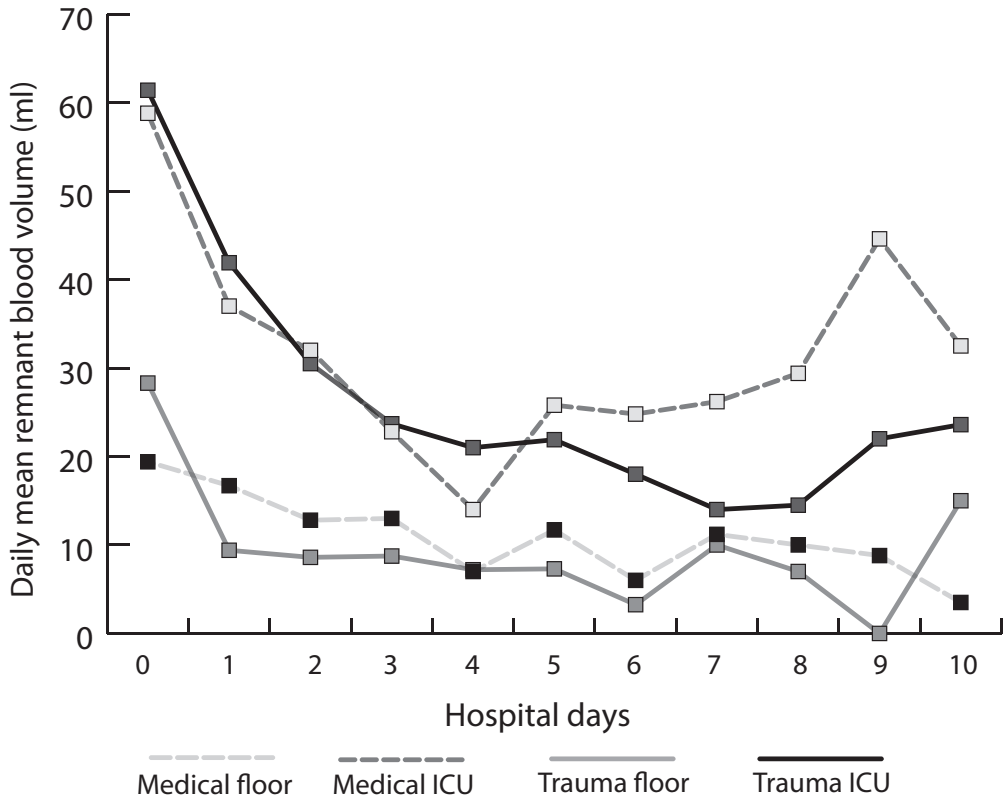
We assessed group comparisons between the emergency department discharge groups using chi-square or Fisher's exact tests for categorical data or nonparametric one-way ANOVA (Kruskal-Wallis) with post-hoc comparisons using the Dwass-Steel-Critchlow-Fligner test for nonnormally distributed continuous data. Comparisons between the ICU groups and the floor groups and between the medical-ICU and the trauma-ICU groups

Table 1.
Subject Characteristics of Floor vs. ICU Patients: Medians (IQRs)

	All *N = 122*	*ICU* *N = 50*	*Floor* *N = 47*	*P-value*
Age (years)	52.5 (46.8, 53.2)	53 (45, 55.6)	57 (47.5, 58.4)	0.38
% male	44 (47%)	27 (56%)	17 (38%)	0.07
Length of stay (days)	5 (5.7, 9.5)	8.5 (9.7, 17.5)	4 (4.2, 6.7)	< 0.0001
Blood remnant, daily (ml)	11.6 (12.3, 15.2)	12.9 (13.1,16.9)	9.8 (9, 12.6)	< 0.001
Blood remnant cumulative (ml)	38.9 (58.5, 118.9)	78.1 (97.6, 222)	24.2 (25.8, 40.5)	< 0.0001
Transfusion daily	0 (0.04, 0.11)	0 (0.07, 0.23)	0 (0.005, 0.07)	< 0.01
Transfusion cumulative	0 (0.54, 2.3)	0 (1.1, 5.4)	0 (0.03, 0.48)	< 0.01
Episodes of Hgb < 7	0 (0.24, 0.69)	0 (0.36, 1.3)	0 (0.03, 0.36)	0.03

IQR = interquartile range; Hgb = hemoglobin

Figure 1.
Daily Remnant Blood Volume Calculated: Volume per Number of Hospital Days



Although data were recorded throughout the entirety of each patient's hospitalization, this figure represents data from the first ten days of hospitalization.

were assessed using two-sample t-tests or Wilcoxon rank sum tests for continuous data and chi-square or Fisher's exact tests for categorical data. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

STUDY RESULTS

Information from a total of 122 patients was included in the final analysis (secondary to duplicate recordings of three patients in the initial data set): 20 trauma-floor patients, 28 trauma-ICU patients, 27 medical-floor patients, 22 medical-ICU patients, and 25 patients discharged from the emergency department. (Two disposition-based groups had greater than 25 patients, as the disposition originally recorded for certain patients was found to be incorrect on further review of the data.) Of the patients included in the study, 50 were admitted to the ICU, 47 total were admitted to the medical and trauma floors, and 25 were discharged (see table 1). The demographics, daily median volumes of remnant blood, and lengths of stay are presented in table 1 and figure 1. The different disposition-based groups demonstrated significant differences in age and no significant difference in sex; there were no significant differences in age, sex, or daily remnant blood volume in ICU patients with respect to the admitting service (see table 2).

The median daily remnant blood volume was 11.6 (interquartile range [IQR]: 12.3, 15.2) ml for all patients. There were significant differences in the volumes of daily median remnant blood when comparing patients based on the level of care they required (ICU vs. floor), as indicated in table 1. Patients admitted to the ICU had significantly higher median daily (12.9 ml vs. 9.8 ml; $p < 0.001$) and cumulative (78.1 ml vs. 24.2 ml; $p < 0.0001$) remnant blood volumes compared to patients admitted to the medical and trauma floors. The cumulative remnant blood volume included the remnant blood volume from the entire admission, with a median length of

Table 2.
Subject Characteristics and Emergency Department Disposition Group: Mean ± SD

	ED discharge N = 25	*Medical floor N = 27*	*Medical ICU N = 22*	*Trauma floor N = 20*	*Trauma ICU N = 28*	*P-value*
Age (years)	42.9 (SD = 14.9)	58.4 (SD =13.7)	54.6 (SD = 14.6)	46.2 (SD = 20.7)	46.8 (SD = 20.5)	0.04**
% male	15 (60%)	8 (32%)	12 (54%)	9 (45%)	15 (58%)	0.27
Daily blood remnant average	20.5 (SD = 11.5)	10.9 (SD = 7.2)	13.9 (SD = 8)	10.6 (SD = 3.9)	15.9 (SD = 5.3)	< 0.001*
Length of stay (days)	NA	5.5 (SD = 5.1)	14.4 (SD = 18.2)	5.5 (SD = 2.8)	12.9 (SD = 9.3)	< 0.0001‡

*For the medical floor vs. trauma ICU, p = 0.001, and for the trauma floor vs. trauma ICU, p = 0.003.
**For emergency department (ED) discharge vs. medical floor, p = 0.006.
‡ For medical floor vs. medical ICU, p = 0.003; for medical floor vs. trauma ICU, p = 0.001; and for trauma floor vs. trauma ICU, p = 0.01.
SD = standard deviation

stay of 5 (IQR: 5.7, 9.5) days for all patients. The median length of stay for patients in the ICU was 8.5 (IQR: 9.7, 17.5) days.

DISCUSSION

In an analysis of medical record information from 122 patients at an academic medical center, we found that the daily remnant blood volume was 11.6 (IQR: 12.3, 15.2) ml for all patients and 12.9 (IQR: 13.1, 16.9) ml for patients admitted to the ICU. A comparison of our medical-ICU daily remnant blood-volume data with published results reveals a similar amount of remnant diagnostic blood (13.9 ml/day vs. 13 ml/day).[6] A comparison of our trauma-ICU daily remnant blood volume data with published results from a surgical ICU reveals a lower diagnostic blood loss in our study (15.9 ml/day vs. 26 ml/day).[7] In comparison with previously published literature, the accepted daily remnant blood volume for patients requiring ICU-level of care is likely 12.9 ml or greater.

In this analysis, we found that the cumulative remnant blood volume (throughout the entirety of the patients' stays) was 38.9 (IQR: 58.5, 118.9) ml for all patients (median length of stay: 5 days [IQR: 5.7, 9.5]) and 78.1 (IQR: 97.6, 222) ml for patients admitted to the ICU (median length of stay: 8.5 [IQR: 9.7, 17.5]). In comparison with data on trauma patients published by Branco et al. in 2009, the cumulative volume in our study is less (38.9 mL vs. 187.3 mL).[8] The cumulative remnant blood volume is also lower for our trauma-ICU data than for previously published trauma-ICU literature.[9] While it is unclear if the decrease in cumulative volume observed between two single-center studies represents different practice patterns between institutions or evolving practice patterns over time, Branco et al. evaluated the entire phlebotomy burden, not remnant blood volume, which likely contributed to the difference in findings. Given our findings and the previously published data, a reasonable cumulative blood-draw volume for a study to qualify for IRB expedited review of research protocols would be as great as 78.1 ml in the ICU population and 38.9 ml in all patients over the course of the entire admission.

Both the daily median remnant blood volume (12.9 ml) and the cumulative remnant blood volume (78.1 ml) in the ICU population would allow for more than 50 ml of blood to be drawn over eight weeks, exceeding the current maximum amount of blood that can be collected from participants under the OHRP guidelines regarding expedited review for minimal risk research. Given that the length of stay for all patients (5 days [IQR: 5.7, 9.5]) is much less than eight weeks, minimal risk guidelines for inpatient studies should be based on daily rather than cumulative blood-draw volumes.

While we believe that the quantitative strategy and prospective approach were strengths of our study, the study also had limitations. The results are based off a consecutive prospective collection of data from rem-

nant blood samples in the clinical laboratory throughout a short period in a single academic center. This could reflect institutional preference at this one center and, given the short duration of the study collection and that providers frequently attend to patients for a week at a time at our institution, could also reflect inpatient provider preference. For generalizability, we included patients from medical services, from trauma services, and those discharged from the emergency department.

CONCLUSION

In the analysis of 122 patients at an academic medical center, we found that the median daily remnant blood volume was 11.6 ml and the median cumulative remnant blood volume was 38.9 ml for all patients with a length of stay of five days. Patients admitted to the ICU from the emergency department had a daily remnant blood volume of 12.9 ml and a cumulative remnant blood volume of 78.1 ml, with a median length of stay of 8.5 days. Our data suggest that currently allowable blood-volume limits to qualify for expedited review for not more than minimal risk research are less than what patients experience in routine clinical testing. Interpretation of findings from this prospective observational study should be limited to the description of remnant blood volume. ♦

SUPPORTING INFORMATION

The appendices are available in the "Supporting Information" section for the online version of this article and via *Ethics & Human Research*'s "Supporting Information" page: https://www.thehastingscenter.org/supporting-information-ehr/.

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