

HHS Public Access

Author manuscript *South Med J.* Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

South Med J. 2016 July ; 109(7): 402–407. doi:10.14423/SMJ.00000000000485.

Examining Invasive Bedside Procedure Performance at an Academic Medical Center

Cynthia Kay, MD, MS, Erica M. Wozniak, MS, Aniko Szabo, PhD, and Jeffrey L. Jackson, MD, MPH

Center for Patient Care and Outcomes Research, Medical College of Wisconsin, Milwaukee

Abstract

Objectives—Explore the performance patterns of invasive bedside procedures at an academic medical center, evaluate whether patient characteristics predict referral, and examine procedure outcomes.

Methods—This was a prospective, observational, and retrospective chart review of adults admitted to a general medicine service who had a paracentesis, thoracentesis, or lumbar puncture between February 22, 2013 and February 21, 2014.

Results—Of a total of 399 procedures, 335 (84%) were referred to a service other than the primary team for completion. Patient characteristics did not predict referral status. Complication rates were low overall and did not differ, either by referral status or location of procedure. Model-based results showed a 41% increase in the average length of time until procedure completion for those referred to the hospital procedure service or radiology (7.9 vs 5.8 hours; P < 0.05) or done in radiology instead of at the bedside (9.0 vs 5.8 hours; P < 0.001). The average procedure cost increased 38% (\$1489.70 vs \$1023.30; P < 0.001) for referred procedures and 56% (\$1625.77 vs \$1150.98; P < 0.001) for radiology-performed procedures.

Conclusions—Although referral often is the easier option, our study shows its shortcomings, specifically pertaining to cost and time until completion. Procedure performance remains an important skill for residents and hospitalists to learn and use as a part of patient care.

Keywords

bedside procedures; hospital medicine; general internal medicine; residents

In the United States, it previously was mandatory for internal medicine residents to perform a minimum number of paracenteses, thoracenteses, and lumbar punctures as part of their training. This changed in 2007, when the American Board of Internal Medicine revised the procedure requirements.¹ Instead of focusing on the performance of procedures, the goal now was to achieve competency in the procedures' indications, contraindications, and complications.²

To purchase larger reprint quantities, please contact reprints@wolterskluwer.com

Correspondence to Dr Cynthia Kay, Center for Patient Care and Outcomes Research, Medical College of Wisconsin, 8701 W Watertown Plank Rd, Milwaukee, WI 53226. ckay@mcw.edu.

The remaining authors have no financial relationships to disclose and no conflicts of interest to report.

One reason for the revision in procedure training was the general consensus that internists seldom perform procedures. This has long been the assumption, supported by a study of national Medicare data.³ Little is known, however, about the number of procedures that internists at academic medical centers actually encounter and perform.

Although no longer obligated to perform them, residents and hospitalists still manage and care for patients requiring these procedures. This became a patient care issue, particularly for residents. Their lack of comfort in performing procedures unsupervised, in addition to time restrictions with new duty-hour rules, contributed to the formation of hospital procedure services (HPS).^{4–7} The HPS at our institution is a hospitalist-run inpatient consult that performs a variety of procedures at the bedside. It is staffed by a hospitalist and can have a single resident on the elective each month. Services are available weekdays during normal business hours.

The amount of research is limited on the outcomes of common invasive bedside procedures by referral status and location of procedure. Referred procedures are those completed by either radiology or the HPS, and the location of the procedure is either bedside or radiology. The few studies completed have compared either primary team and HPS⁸ or bedside and radiology,⁹ finding no differences in complication rates. Also, little information exists on the impact, if any, that patient characteristics have on referrals.

The primary objectives of our study were to determine the procedure performance pattern at an academic medical center, evaluate whether patient characteristics predict referral, and compare the clinical outcomes of lumbar punctures, paracenteses, and thoracenteses by location and service.

Methods

Design

A cross-sectional, 1-year, prospective observational design was created to determine the number of paracenteses, thoracenteses, and lumbar punctures completed for hospitalized patients admitted to an internal medicine service. Subsequently, a retrospective chart review was conducted to examine the clinical outcomes of the procedures identified in the previous year.

Site and Subjects

The study was conducted at Froedtert Hospital, a tertiary academic medical center located in Milwaukee, Wisconsin and was approved by the Medical College of Wisconsin institutional review board. Patients were hospitalized adults admitted to a medical service who underwent a thoracentesis, paracentesis, or lumbar puncture between February 22, 2013 and February 21, 2014. Patients were identified daily for 1 year through a platform associated with our institution's electronic medical record. We excluded outpatient procedures, those done in the emergency department, or those ordered by a service other than the primary team. We also excluded central lines and procedures done in the medical intensive care unit (ICU). At our institution, the medical ICU is a closed unit, and the HPS does not perform procedures there. Central lines also are not placed on the general medicine floors.

A chart review abstracted patient characteristics (age; sex; presence of kidney, liver, hematologic or infectious disease; body mass index; use and type of anticoagulation; international normalized ratio value; presence of delirium; use of empiric antibiotics; primary team); procedure characteristics (procedure, service performing procedure, time until completion, cost); admission characteristics (day and time of admission, length of stay); and complications (immediate and delayed). The specific comorbidities were chosen because they usually have some influence on procedures. Chart reviews were done by a single investigator (C.K.).

Use of anticoagulation was defined as having received full-dose aspirin (324 or 325 mg), warfarin, clopidogrel, direct thrombin or factor Xa inhibitor, or any therapeutic dose of low-molecular-weight heparin or heparin product within 24 hours before the procedure.

Immediate complications were defined as pneumothorax, hemothorax, pneumoperitoneum, hemoperitoneum, hypotension, uncontrolled bleeding, and uncontrolled postprocedure pain. Delayed complications included transfer to the ICU, infection at procedure site, and bleeding beyond 2 hours postprocedure. Time until completion was defined as the time from the initial decision that the procedure was needed to when the procedure was finished. This information was determined through order history in the electronic medical record. Procedure costs were only the hospital's charges and did not include physicians' or other professional fees. Costs were obtained by itemized lists from the billing department, which included all medications, equipment, and imaging obtained specifically for the procedure.

Analysis

Procedure Pattern—Descriptive statistics are presented as counts and means for categorical and continuous variables, respectively, by referral status. Univariate analyses used Fisher exact tests for categorical outcomes and *t* tests for continuous outcomes. The service that performed the procedure was initially divided into four groups: resident team, hospitalist, HPS, and radiology. These were then collapsed into two groups: first, by referral status (radiology and HPS as referred; resident team and hospitalist as not referred), and second, by location (bedside vs radiology). The groups were categorized in this manner in an attempt to determine whether operator (specialist vs internist) and location are important factors in procedure outcomes.

The predictors were assessed jointly in a multivariable logistic regression model on referral status (referred vs not referred), built using backward elimination, with P < 0.2 fixed as a cutoff for remaining in the model. To control for primary service, only patients with a primary resident team were included in the regression (N = 288) because nearly all hospitalists referred procedures. Independent variables included the service to which the patient was admitted; the patient's age; time and day of admission; presence of kidney, liver, hematologic, or infectious disease; body mass index, use of anticoagulation, international normalized ratio value, and empiric use of antibiotics.

Procedure Outcomes—To assess procedure outcomes, immediate and delayed complications were combined to create a binary indicator for the occurrence of complications that served as the primary outcome of interest in the second part of the study.

Procedure cost, length of hospitalization, and time from the decision to perform a procedure until its completion were secondary endpoints. Logistic regression was used to create a propensity score model that matched referred and nonreferred as well as bedside and radiology patients according to demographic and clinical characteristics. The propensity score matching was used to control for observable confounders. Following propensity matching, logistic regression was used to examine whether referral or having procedures performed in radiology were predictive of the occurrence of complications (yes/no), and odds ratios were calculated along with 95% confidence intervals. Linear regression was used to examine the relation between referral and bedside procedures and each secondary endpoint. The length of hospitalization, time to procedure, and procedure cost outcomes were log-transformed to satisfy normality assumptions. Subsequently, the regression coefficients of interest were back-transformed to obtain effect sizes that represent a percentage increase in the average value of the outcome.¹⁰

Data were entered into Research Electronic Data Capture, which is a secure, Web-based application designed to support data capture for research studies.¹¹ All of the analyses were performed in STATA 12.1 (StataCorp, College Station, TX) and the MatchIt package in R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In 1 year, a total of 399 procedures were attempted, with 391 completed. Most were thoracentesis (n = 168, 42%), followed by paracentesis (n = 164, 41%), and lumbar puncture (n = 67, 17%). Overall, most procedures (84%) were referred either to radiology (56%, n = 222) or the HPS (28%, n = 113). Referral frequency was similar for each type of procedure: lumbar puncture 84% (n = 56), thoracentesis 87% (n = 146), and paracentesis 81% (n = 133). Resident-run teams cared for most of the patients requiring procedures (n = 288, 72%). The average age of patients was 58 years (range 19–96).

Hospitalists performed significantly fewer procedures (n = 5, 5% vs n = 59, 20%) than did residents (P < 0.001). Patients of obesity class II and higher were more likely to be referred (94%) compared with overweight and below (83%) and obesity class I (77%; P = 0.03). No significant differences were found by type of procedure (P = 0.34), day of week (P = 0.67), time of admission (P = 0.10), or other patient characteristics (Table 1), however. Multivariable analysis found that no variable was significant in predicting referral (Table 2).

There was a complication rate of 7% (n = 27). For the primary outcome of complications, logistic regression using propensity score matching found no difference in the risk of complications by referral status (referred n = 23 vs not referred n = 4; P= 0.62) or location of procedure (radiology n = 13 vs bedside n = 14; P= 0.41; Table 3); however, the study was underpowered to detect such differences because of the low rate of complications. For the continuous secondary outcomes, the mean length of stay for referred procedures was 12.5 (standard deviation [SD] 15.4) days compared with 12.0 (SD 18) days for procedures that were not referred. Neither referral nor location of procedure had a significant effect on the length of hospitalization.

The mean time until procedure completion was 7.9 (SD 10.6) hours for referred procedures and 5.8 (SD 9.8) hours for nonreferred procedures. For radiology-performed procedures, the mean time until procedure completion was 9.0 (SD 11) hours, compared with 5.8 (SD 9.5) hours for bedside procedures. Our study found that both referral and radiology-performed procedures increased the length of time until procedure completion (P < 0.05 and P < 0.001, respectively). Controlling for demographic and clinical characteristics, our models suggest that either procedure referral or location change results in an approximately 41% increase in the average time until the procedure is performed. This translates to approximately 3 additional hours of waiting from an average of 5.8 hours. The mean cost of referred procedures was \$1489.70 (SD 834.70) compared with \$1023.30 (SD 575.30) for those not referred. The mean cost of radiology-performed procedures was \$1625.77 (SD 806.88), in contrast to \$1150.98 (SD 751.18) for those done at the bedside. Referral and location change both significantly increased the cost of procedures (P < 0.05; Table 4). Controlling for patient characteristics, model-based results show that referred and radiology-performed procedures resulted in respective cost increases of 56% and nearly 38% from the average cost of not referred and bedside procedures. This translated to an additional expense of \$400 to \$600 per procedure.

Discussion

Although the general assumption has been that internists perform few procedures, limited studies have quantified the number of procedures encountered and referred. Our study found that both residents and hospitalists refer the majority of the procedures they encounter. This is consistent with Medicare data that suggests that radiology performs most of the procedures.³

Interestingly, we found that patient characteristics did not generally predict referral status. The inability of comorbidities commonly associated with higher risks to predict referral also was noted by Barsuk and colleagues.⁹ This suggests that providers are more concerned about other factors, such as time and logistics, when deciding to perform a procedure. Alternatively, perhaps it implies that providers refer procedures regardless of comorbidities and other potential influencers simply because it is easier.

Referral and change of location to radiology both were found to significantly increase the time until procedure completion as well as procedure cost. These results logically make sense because primary teams generally have the best access to their patients to perform procedures without much delay. Radiology and the HPS are limited in that they are available only during weekday business hours. Even though technically radiology is staffed around the clock, priority is given to emergent and urgent cases outside normal work hours.

The price for radiology-performed procedures is understandably higher compared with those done by internists at the bedside because there are charges for specific equipment, specialists' time, and dedicated procedure space. Our study focused on the hospital costs and not the price to the patient; however, one can assume that the charges to the patient would be even higher. Barsuk et al also found hospital costs to be lower when the procedure was

performed by medicine, gastroenterology, or hepatology as compared with interventional radiology.¹²

The lack of differences in complications of invasive bedside procedures by either referral status or location of the procedure was an important finding. Unfortunately, given the overall low rate of complications, this result is uninterpretable. Despite this, it is still worth mentioning that the continuing belief is that procedures performed in radiology are safer than those done at the bedside. This assumption prevails even without supportive evidence.

The difference in cost for procedures done at the bedside compared with by radiology was significant and raises concerns with the continued rise in healthcare costs the nation faces. Some offered explanations for the soaring costs include the use of technology, treatment not proven to be more effective over other methods, and the total spending for each hospitalization.^{13–15} Bedside procedures may be an illustrative example.

In addition to the impact on healthcare costs, the results may have a significant impact on residency training and hospitalist requirements. Specifically, the results may suggest the need for increased procedural training and improved procedure curriculum for residents and possibly hospitalists. The Society of Hospital Medicine endorses nine bedside procedures, including the three in our study, as core competencies.¹⁶ In general, hospitalists are not required to perform all nine procedures; their responsibilities depends on their hospital of employment. Perhaps our findings allude to the idea that hospitalists should be expected to perform procedures, however.

Procedure performance may be particularly important in rural and community hospitals. Research has shown that internists in rural settings are more likely to perform procedures as compared with their urban counterparts.¹⁷ This is likely because of a lack of resources or available staff and subspecialties such as critical care medicine and interventional radiology. In fact, the shortage of intensivists has required some hospitalists, particularly in the community, to care for patients in the ICU and perform procedures that would normally be done by critical care specialists in a closed unit.^{18–20}

In an urban academic hospital, hospitalists may not feel pressured to perform procedures. Many may believe their time is better spent on intellectual tasks and that reimbursement is insufficient for the time needed to perform them²¹; however, hospitalists often supervise and train residents, whose experience with procedures frequently are tied to those of their attending. A study showed that residents on a hospitalist-staffed service believed their overall educational experience was better compared with a traditionally staffed service.²² The possible explanation for this was that having on staff an attending who did not have other clinical duties offered more opportunity and time for teaching. It would then seem natural that those with more time with trainees would have a better chance to train and develop their procedural skills instead of referring to other services.

There are a number of limitations to our study. First, it was conducted at a single academic institution. It is uncertain whether our findings can be generalized to other academic institutions, communities, or rural hospitals. Also, although statistically significant, whether the differences in time until procedure completion and cost by referral status and location are

clinically relevant is debatable. One may argue that waiting 3 additional hours for a radiology-performed procedure is not meaningful. Furthermore, the study was underpowered to detect differences in complication rates by referral status or location because of the overall small number of complications.

Conclusions

At our academic medical center, residents and hospitalists perform few procedures. Referred procedures and those performed by radiology were associated with increased cost and time until completion, compared with those done at the bedside by the primary team. Future, appropriately powered studies are needed to draw outcome conclusions. Our findings suggest that procedure training remains important and strongly advise the need to reexamine current procedure practices.

Acknowledgments

This project was funded by the Patient-Centered Outcomes Research Program (PCORP) through the Research and Education Program Fund, a component of the Advancing a Healthier Wisconsin endowment at the Medical College of Wisconsin and by National Research Service Award grant no. T 32 HP 10030.

C.K. has received a Medical College of Wisconsin Center for Patient Care and Outcomes Research seed grant. A.S. is supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant no. 8UL1TR000055.

References

- Duffy FD, Holmboe ES. What procedures should internists do? Ann Intern Med. 2007; 146:392– 393. [PubMed: 17339625]
- American Board of Internal Medicine. Internal medicine policies. http://www.abim.org/certification/ policies/imss/im.aspx#procedures. Accessed May 14, 2015
- 3. Duszak R Jr, Chatterjee AR, Schneider DA. National fluid shifts: fifteen-year trends in paracentesis and thoracentesis procedures. J Am Coll Radiol. 2010; 7:859–864. [PubMed: 21040867]
- Lenhard A, Moallem M, Marrie RA, et al. An intervention to improve procedure education for internal medicine residents. J Gen Intern Med. 2008; 23:288–293. [PubMed: 18214624]
- Mourad M, Ranji S, Sliwka D. A randomized controlled trial of the impact of a teaching procedure service on the training of internal medicine residents. J Grad Med Educ. 2012; 4:170–175. [PubMed: 23730437]
- Mourad M, Kohlwes J, Maselli J, et al. Supervising the supervisors—procedural training and supervision in internal medicine residency. J Gen Intern Med. 2010; 25:351–356. [PubMed: 20077049]
- 7. Huang GC, Smith CC, Gordon CE, et al. Beyond the comfort zone: residents assess their comfort performing inpatient medical procedures. Am J Med. 2006; 119:71.e17–e24. [PubMed: 16431194]
- Tukey MH, Wiener RS. The impact of a medical procedure service on patient safety, procedure quality and resident training opportunities. J Gen Intern Med. 2014; 29:485–490. [PubMed: 24272831]
- 9. Barsuk JH, Cohen ER, Feinglass J, et al. Clinical outcomes after bedside and interventional radiology paracentesis procedures. Am J Med. 2013; 126:349–356. [PubMed: 23398950]
- Vittinghoff, E.; Glidden, DV.; Shiboski, SC., et al. Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models. New York: Springer Science & Business Media; 2012.
- Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadatadriven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–381. [PubMed: 18929686]

- Barsuk JH, Feinglass J, Kozmic SE, et al. Specialties performing paracentesis procedures at university hospitals: implications for training and certification. J Hosp Med. 2014; 9:162–168. [PubMed: 24493399]
- Robert Wood Johnson Foundation. What are the biggest drivers of cost in US health care?. http:// www.rwjf.org/content/dam/farm/reports/issue_briefs/2011/rwjf71331. Published July 2011. Accessed February 5, 2015
- Leavitt, C. Panel: medical technology behind high health care costs. http:// www.commonwealthfund.org/publications/newsletters/washington-health-policy-in-review/ 2008/oct/washington-health-policy-week-in-review—october-20–2008/panel-medical-technologybehind-high-health-care-costs. Published October 20, 2008. Accessed February 5, 2015
- Schoenman, JA.; Chockley, N. Understanding US health care spending. www.nihcm.org/images/ stories/NIHCM-CostBrief-Email.pdf. Accessed February 5, 2015
- Butterfield, S. Core competencies peripheral in practice. http://www.acphospitalist.org/archives/ 2010/08/qa.htm. Published August 2010. Accessed March 30, 2015
- Wigton RS, Alguire P. The declining number and variety of procedures done by general internists: a resurvey of members of the American College of Physicians. Ann Intern Med. 2007; 146:355– 360. [PubMed: 17339620]
- Angus DC, Kelley MA, Schmitz RJ, et al. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? JAMA. 2000; 284:2762–2770. [PubMed: 11105183]
- Siegal EM, Dressler DD, Dichter JR, et al. Training a hospitalist workforce to address the intensivist shortage in American hospitals: a position paper from the Society of Hospital Medicine and the Society of Critical Care Medicine. J Hosp Med. 2012; 7:359–364. [PubMed: 22605535]
- 20. Heisler M. Hospitalists and intensivists: partners in caring for the critically ill—the time has come. J Hosp Med. 2010; 5:1–3. [PubMed: 20063392]
- Thakkar R, Wright SM, Alguire P, et al. Procedures performed by hospitalist and non-hospitalist general internists. J Gen Intern Med. 2010; 25:448–452. [PubMed: 20195784]
- 22. Chung P, Morrison J, Jin L, et al. Resident satisfaction on an academic hospitalist service: time to teach. Am J Med. 2002; 112:597–601. [PubMed: 12015263]

Author Manuscript

Key Points

- Patient characteristics did not predict whether a procedure was referred for completion.
- Internal medicine residents and hospitalists refer the majority of bedside procedures they encounter.
- Referred bedside procedures take a longer time to complete and cost more compared with nonreferred procedures.

Table 1

Comparison of patient characteristics by referral status

Variable	Referred (n = 335)	Not referred (n = 64)	Р
Age, y, mean (SD)	59 (SD 18)	57 (SD 17)	0.34
Sex, n (%)			0.22
Male	184 (82)	41 (18)	
Female	151 (87)	23 (13)	
Primary team, n (%)			< 0.001
Teaching team, n (%)	229 (80)	59 (20)	
Hospitalist	106 (95)	5 (5)	
Procedure, n (%)			0.34
Paracentesis	133 (81)	31 (19)	
Lumbar puncture	56 (84)	11 (16)	
Thoracentesis	146 (87)	22 (13)	
Time of admission ^b , n (%)			0.10
Daytime	164 (81)	39 (19)	
Overnight	171 (87)	25 (13)	
Day of admission ^{<i>a</i>} , n (%)			0.67
Weekday	214 (83)	43 (17)	
Weekend	121 (85)	21 (15)	
Kidney disease, n (%)			0.20
None	170 (85)	30 (15)	
ESRD	24 (73)	9 (27)	
CKD, other	141 (85)	25 (15)	
Liver disease, n (%)			0.08
None	196 (87)	30 (13)	
Cirrhosis	107 (83)	22 (17)	
Noninfectious hepatitis, other	32 (73)	12 (27)	
Hematologic abnormality, n (%)			0.79
Anemic or no abnormality	176 (83)	35 (17)	
Abnormality 2 cell lines, malignancy	159 (85)	29 (15)	
Infectious disease, n (%)			0.75
None	259 (84)	51 (16)	
Yes	76 (85)	13 (15)	
BMI, n (%)			0.03
Overweight or below	227 (83)	46 (17)	
Obesity class I	48 (77)	14 (23)	
Obesity class II and above	59 (94)	4 (6)	
Anticoagulation, n (%)			0.86

Variable	Referred (n = 335)	Not referred (n = 64)	P
None	277 (84)	54 (16)	
Yes	58 (85)	10 (15)	
INR, n (%)			0.97
1.5	258 (84)	49 (16)	
1.6–2.0	44 (83)	9 (17)	
2.1	33 (84)	6 (15)	
Antibiotic started before procedure, n (%)			0.40
No	126 (82)	28 (18)	
Yes	209 (85)	36 (15)	
Presence of delirium, n (%)			0.54
None	242 (83)	49 (17)	
Yes	93 (84)	15 (14)	

BMI, body mass index; CKD, chronic kidney disease; ESRD, end-stage renal disease; INR, international normalized ratio; SD, standard deviation.

^aWeekday is Monday-Thursday.

^bDaytime is 7 AM–6 PM.

Table 2

Model-based ORs for procedure referral

Independent variable	OR (95% CI) of being referred for a procedure	Р
Liver disease		0.12
None	Referent	
Cirrhosis	0.86 (0.45–1.69)	
Noninfectious hepatitis, other	0.41 (0.17–0.98)	
BMI		0.05
Overweight or under	Referent	
Obesity class I	0.58 (0.28–1.26)	
Obesity class II and above	2.70 (0.98–9.65)	
Time of admission		0.09
Daytime	Referent	
Overnight	1.69 (0.93–3.10)	
Age, y	1.01 (0.99–1.03)	0.11

The data in the table were derived from a backward stepwise logistic regression model. BMI, body mass index; CI, confidence interval; OR, odds ratio.

Page 13

Table 3

Complications (N = 23) by referral status and location

Complications, n (%)	Referred	Not referred	Radiology	Bedside
Immediate	10 (77)	3 (23)	5 (38)	8 (62)
Delayed	13 (93)	1 (7)	8 (57)	6 (43)

Table 4

Clinical outcomes by referral status and location

Outcome	Referred procedure	Radiology procedure
Complications ^a OR (95% CI)	0.77 (0.29–2.35)	0.68 (0.27–1.69)
Time until procedure b	41.3 ^c	41.4 ^d
Length of stay ^b	21.3	15.6
Cost of procedure ^b	56.2 ^d	37.8 ^d

CI, confidence interval; OR, odds ratio.

^aLogistic regression.

 $b_{\rm Linear}$ regression, log-transformed outcome. Model-based percentage increase in average outcome value.

 $C_{P < 0.05.}$

 $d_{P < 0.001.}$