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Cardiopulmonary ultrasound for critically ill adults improves diagnostic accuracy in a resource-limited setting: the AFRICA trial

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ABSTRACT

Objective: To assess the effects of a cardiopulmonary ultrasound (CPUS) examination on diagnostic accuracy for critically ill patients in a resource limited setting.

Methods: Approximately half of the emergency medicine resident physicians at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana were trained in a CPUS protocol. Adult patients triaged to the resuscitation area of the emergency department (ED) were enrolled if they exhibited signs or symptoms of shock or respiratory distress. Patients were assigned to the intervention group if their treating physician had completed the CPUS training. The physician's initial diagnostic impression was recorded immediately after the history and physical examination in the control group, and after an added CPUS examination in the intervention group. This was compared to a standardized final diagnosis derived from post-hoc chart review of the patient's care at 24 hours by two blinded, independent reviewers using a clearly defined and systematic process. Secondary outcomes were 24-hour mortality and use of IV fluids, diuretics, vasopressors and bronchodilators.

Results: Of 890 patients presenting during the study period, 502 were assessed for eligibility, and 180 patients were enrolled. Diagnostic accuracy was higher for patients who received the CPUS examination (71.9% vs. 57.1%, Δ 14.8% [CI 0.5%, 28.4%]). This effect was particularly pronounced for patients with a

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“cardiac” diagnosis, such as cardiogenic shock, congestive heart failure, or acute valvular disease (94.7% vs. 40.0%, Δ 54.7% [CI 8.9%, 86.4%]). Secondary outcomes were not different between groups.

Conclusions: In an urban ED in Ghana, a CPUS examination improved the accuracy of the treating physician’s initial diagnostic impression. There were no differences in 24-hour mortality and a number of patient care interventions.

Keywords: Sonography; Global Health; Africa; Critical Illness; Dyspnea; Shock

INTRODUCTION

Shock and respiratory distress are frequently encountered symptoms of critical illness in the emergency department (ED) and are associated with high mortality rates in both high- and low-income countries.(1-4) These conditions are challenging to manage, because the differential diagnosis is broad and treatment strategies vary greatly based on underlying etiology. Early and accurate diagnosis is essential during the initial resuscitation.(5) ED management of critically ill patients in low- and middle-income countries (LMICs) has many unique challenges, as resources such as laboratory tests, advanced imaging, and medications are not always available.

In high-income countries, ultrasound is increasingly being utilized by emergency physicians (EPs) during the initial evaluation of critically ill patients presenting with undifferentiated symptoms, in order to more quickly arrive at an accurate diagnosis. Several ultrasound protocols have been developed to assist in the assessment of shock(6-8) and respiratory distress,(9-11) incorporating examinations of the heart, lungs, and abdomen, in addition to other organ systems. Ultrasound has been shown to improve diagnostic accuracy, change management(12-15) and may reduce mortality rates(16) for critically ill patients. Although there have been several studies demonstrating the feasibility of ultrasound training in LMICs,(17-19) evidence on the impact of ultrasound on emergency care in such settings is limited.(20-22)

We hypothesized that a cardiopulmonary ultrasound (CPUS) protocol would improve diagnostic accuracy in patients with signs of shock or respiratory distress presenting to an emergency department in Ghana.

METHODS

Study Design and Setting

This was a prospective observational cohort study in the Accident and Emergency Centre (ED) at Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana. Approximately 27 million people live in Ghana and Kumasi’s population approaches 2.1 million. The average life expectancy in Ghana is 66.6 years. In 2016, Ghana’s economy ranked 85th among a total of 195.(23, 24) KATH is home to West Africa’s only emergency medicine residency training program. It is a major referral center in the region with 1200 beds. Close to 29,000 patients are seen in the ED at KATH each year and approximately 30% are critically ill.

Upon arrival at the KATH ED, patients are triaged using the South African Triage Score, a scoring system developed in South Africa and since validated in various resource-limited settings. This “triage score” is generated based on the patient’s mobility, respiratory rate, heart rate, systolic blood pressure, temperature, AVPU (alert/verbal/pain/unresponsive) score, and trauma. (25, 26) Patients with more abnormal values for these criteria, receive a higher triage score. Critically ill patients with a score of 7 or more are immediately triaged to the resuscitation area of the emergency department (RED), a large hall with space for 10-12 patients. Patients are then assessed simultaneously by nurses and physicians.

Ultrasound Protocol and Training

As we reported previously, we developed a CPUS examination based on the Rapid Ultrasound in Shock (RUSH)(7) and Bedside Lung Ultrasound in Emergency (BLUE) protocols,(9) integrating scans from the lungs, heart, inferior vena cava (IVC), abdominal cavity, aorta, and femoral veins.(27) Emergency medicine resident physicians were trained in the CPUS protocol and all demonstrated competency prior to study participation. Pathologic findings were recorded and ongoing quality assurance and image/video review were conducted throughout the study period through an online messaging service.

Selection of Participants

Between July 19th, 2016 and January 5th, 2017, all patients presenting to RED were screened for eligibility. Criteria for enrollment included presence of at least one of the following signs or symptoms of shock or respiratory distress: 1) unresponsiveness or altered mental status with Glasgow Coma Scale <13; 2) diaphoresis; 3) capillary refill >3 seconds; 4) systolic blood pressure <100 mmHg at any point between arrival at the ED and intravenous (IV) fluid administration; 5) heart rate >100 beats per minute; 6) respiratory rate >20 breaths per minute; and 7) oxyhemoglobin concentration by pulse oximetry of <92% without supplemental oxygen. Patients were excluded from the study in the following cases: 1) age younger than 18 years, 2) history of chronic low blood pressure as evidenced by patient/family report or prior documentation; 3) acute coronary syndrome as determined by ST segment elevation on EKG; 4) significant resuscitative measures prior to screening (defibrillation, advanced life support medications or mechanical ventilation); 4) determination of etiology of patient’s illness prior to screening (obvious gastrointestinal bleeding or trauma patients); and 6) onset of signs or symptoms of shock or respiratory distress after the initial ED evaluation. Those under the age of 18 were excluded from this study because the CPUS protocol includes evaluations for several diseases (e.g., congestive heart failure, ruptured abdominal aortic aneurysm) that have large differences in prevalence, etiology and natural history of disease between adult and pediatric populations. In addition, the component of the CPUS protocol have not independently been verified in pediatric patient studies.

Study arm assignment and documentation of all study related data were performed by two research assistants (RA) who were present in the ED from 8 am to 8 pm, Monday through Friday, and on 20 days of

24 weekends during the study period. Data were entered into a custom Redcap (Vanderbilt University, Nashville, TN, USA) database. While patients were assessed by their treating physician with a history and physical examination, an RA assessed the patient for eligibility, and if eligible proceeded with study arm assignment. Eligible subjects were assigned to the intervention group when their treating physician had previously received CPUS training, while subjects were assigned to the control group when their treating physician had not received CPUS training.

Measurements

After the initial history and physical examination, the physician caring for a patient in the control group was asked to provide the one most likely diagnosis, which was grouped into diagnostic syndromes by impact on clinical management (Table 1).

For patients in the intervention group, the treating physician was prompted by an RA to provide their differential diagnosis for the etiology of the patient's illness, which could include one or more different diagnoses. Subsequently, the physician performed the CPUS examination using a handheld ultrasound device (VScan Dual; GE Healthcare, Chicago, Illinois, USA). The examination findings were verbally reported to the RA using a pre-defined checklist. The physician was then asked to provide the one most likely diagnosis thought to be responsible for the patient's condition (Figure 1).

An RA followed up at 24 hours if the patient was still in the ED, otherwise follow-up occurred upon discharge, admission to an inpatient unit or the patient's death, whichever event occurred earlier. This follow-up included a review of all paper records, in addition to a face-to-face review with the physician caring for the patient at the time. The RA documented the amount of IV fluids given, whether diuretics, bronchodilators, vasopressors/inotropes had been administered, and whether the patient was alive or dead. Anonymized paper records were scanned and stored electronically.

Outcomes

The primary outcome was the effect of the CPUS examination on diagnostic accuracy. Diagnostic accuracy was defined as whether the physician-reported most likely diagnosis after the initial assessment (history and physical examination, plus CPUS examination in the intervention group) matched the diagnosis at 24 hours in the ED or at disposition from the ED by discharge, admission, transfer or death, whichever occurred earlier, as determined by chart review. The chart review was performed after enrollment had concluded by two board-certified EPs with experience working at KATH and in other LMIC settings. Using a systematic process, these EPs independently reviewed the scanned medical records of the first 24 hours in the ED, and determined the final diagnosis. They were blinded to the study arm assignment and the results of the CPUS. Disagreements were resolved by consensus.

Secondary outcomes were volume of intravenous fluids administered, use of diuretics, vasopressors/inotropes, bronchodilators, use of invasive and non-invasive mechanical ventilation, and 24-hour mor-

tality. All secondary outcomes were recorded during the same 24-hour follow-up as the primary outcome. Baseline diagnostic accuracy was estimated to be at 60%. A sample size of 158 subjects was calculated for a hypothesized absolute improvement by 30%. To allow for potential loss to follow-up, the IRB approved for 180 subjects to be enrolled.

Subject Safety and Ethics

All patients immediately received local standard of care interventions upon arrival to the ED including history and physical examination, and any intervention deemed appropriate by the treating physician. Patient care was not delayed at any point due to study procedures. Informed consent was obtained in parallel to the physician's initial evaluation and prior to any study intervention by the RAs, typically involving next of kin, including a process for non-literate subjects. The study design was reviewed and approved by the Institutional Review Boards of the University of Michigan and the Kwame Nkrumah University of Science and Technology, School of Medical Sciences. The study was registered in the ClinicalTrials.gov registry (NCT02794909).

Statistical Analysis

Data were analyzed using descriptive and frequentist inference statistics using Statistical Analysis System (SAS) version 9.4 (SAS institute, Cary, NC, USA) using an intention-to-treat approach. Categorical data were reported as counts and percentages and were analyzed using the chi-square test. Differences of proportions were used as indices of effect size, and 95% confidence intervals (CI) for effect sizes were calculated using procedures in Agresti and Caffo.(28) For secondary outcomes, Hochberg correction was used to adjust for multiple comparisons.

RESULTS

Twenty emergency medicine resident physicians, ranging from first to third year in residency training, participated in the CPUS training. Of 890 patients admitted to RED during the study period, 502 presented while an RA was on-duty and were screened for eligibility. A total of 180 patients were enrolled in the study, with 94 patients assigned to the intervention group (*Figure 2*).

The mean age of patients in the intervention group was 55 years and 51 years in the control group. Presenting signs/symptoms for both groups are summarized in *Table 2*. Ninety CPUS examinations were performed, and pathologic findings were common. An abnormal LV function was noted in 43 (47.8%) patients and an abnormal lung profile was documented in 38 (42.2%) (*Table 3*). The majority of patients (n=50, 27.8%) had a final diagnosis in the neurologic group, followed by sepsis (n=47, 26.1%) and cardiac causes (n=24, 13.3%) (*Table 4*).

Diagnostic accuracy was higher for patients who received the CPUS examination (71.9%) than those who did not (57.1%; Δ 14.8% [CI 0.5%, 28.4%]) (*Table 5*). The difference was statistically significant and par-

ticularly pronounced in patients with a cardiac diagnosis (Δ 54.7% [8.9%, 86.4%]), and not statistically significant in other subgroups. There were no statistically significant differences between the two groups for any of the other secondary outcome parameters, including 24-hour mortality. Several examples of abnormal ultrasound findings and their clinical context are included in Figure 3.

DISCUSSION

Our study demonstrates that incorporating a CPUS protocol into the initial assessment of critically ill patients presenting to an urban ED in Ghana improved the accuracy of the physician's first diagnostic impression when compared to history and physical examination alone, particularly in those presenting with a cardiac disease. It is well known that the diagnosis of many acute cardiac diseases is difficult(29) and for the diagnosis of pulmonary edema, ultrasound is superior to physical examination findings alone.(30-32) The role of bedside ultrasound for the evaluation of critically ill patients has been established over the last few years in resource-rich environments, but is poorly defined for the LMIC setting where ultrasound use has traditionally focused on obstetrical indications.(33)

Much of the existing literature on ultrasound in LMICs reports on teaching ultrasound skills, subjective impact on management and case reports.(20) Nonetheless, the potential impact is arguably much larger in this environment, where ultrasound may be the only diagnostic tool immediately available, and where patients present late into a disease process. This is corroborated by the high prevalence of pathologic findings in our study cohort, similar to other reports.(21) In addition, it is important that new research and treatments be tailored to the low-resource environment, instead of being automatically accepted as proven interventions.(34) For example, during a study in Zambia on resuscitation for sepsis, researchers ended the trial early after unexpectedly finding a higher mortality rate in patients receiving more aggressive fluid resuscitation.(35)

Our study aimed to more rigorously assess the effects of ultrasound in a low-resource setting by employing a comprehensive CPUS examination covering most major organ systems involved in critical illness, training a large number of physicians as opposed to a few select study ultrasonographers, and by screening all critically ill patients with few exclusion criteria. Additionally, our study was performed over an extended period of time, without constant presence of a supervisory team, and our findings are more likely to be consistent with real-world effect on practice than in a tightly controlled and highly monitored study setting.

We made several decisions impacting our study design. Since test results at KATH do not always return within a reliable timeframe, we chose to record the presumptive diagnosis immediately following the initial assessment and ultrasound examination for intervention group, considering that the initial diagnostic impression typically affects the immediate resuscitation and thus other management decisions long into the patient's hospital course. We also chose to perform a structured post-hoc chart review to determine the 24-hour diagnosis, as opposed to simply relying on the documented diagnosis because of a lack of conformity in diagnosis recording (e.g., no standardized terminology, listing only one contributory diagnosis) and at

times incoherent, illegible or incomplete documentation.

We did not enroll patients at night due to concerns over the personal safety of our research staff, as the research assistants' primary mode of transportation was by foot and the local study partners expressed concerns that it was not safe for them to walk alone at night. While this may have confounded some of our results, it also reflects the difficulties of conducting quality research in an LMIC setting. While the study group assignment was based on presence of a trained physician, study sonographers had been selected randomly and included physicians in various stages of training, thus limiting the potential for bias introduced by this approach.

Despite improved diagnosis, there was no statistically significant difference in secondary outcomes, which focused on patient care interventions. Although differences were in the predicted direction, it is possible that our study was underpowered to demonstrate an effect. However, we believe that the fact that family members are required to purchase medications and laboratory studies at the time they are acutely needed is more likely to have confounded our results. Even if the physician felt strongly that a certain intervention was warranted based on the findings from the CPUS examination, it may still not have been implemented due to a lack of financial means, no family members being available or a lack of resources in the ED.

Conducting clinical research in LMICs is still met with many unique challenges with regards to local infrastructure, staff awareness and familiarity, as well as funding.⁽³⁶⁾ There may be limitations with the physical buildings, electricity, access to internet, available office space, the availability of trained research assistants, ethical oversight committees, and biostatisticians.⁽³⁴⁾ The future direction of research in LMICs, including for ultrasound, should focus on obtaining baseline information about disease burden and patient outcome measures. There is a lack of information on disease burden in the acute care setting for LMICs,⁽³⁷⁾ including for critical illness.⁽³⁸⁾ Continued collaboration between institutions will be an important component of future research efforts.⁽³⁹⁾

In a tertiary ED in Ghana, a CPUS examination performed immediately after an initial history and physical examination improved the accuracy of the treating physician's initial diagnostic impression, specifically in patients with a cardiac etiology for their illness. There were no differences in 24-hour mortality and a number of patient care interventions between the intervention and control group, possibly due to existing limitations at the study site.

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Table 1: Diagnostic syndromes

Diagnostic syndrome	Examples of potential conditions in this group
Neurologic	Stroke, intracranial hemorrhage, seizure, and hypertensive encephalopathy
Sepsis	Sepsis, septic shock, systemic infection
Cardiac	Congestive heart failure exacerbation, cardiogenic shock, acute coronary syndrome, arrhythmias, acute valvular disease, cardiomyopathy
Endocrine	Diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, hypoglycemia
Hepatic	Acute liver failure, sequelae of chronic hepatitis
Renal	Acute renal failure, exacerbation of chronic renal failure, hyperkalemia
Acute abdomen	Acute appendicitis, acute cholecystitis, cholangitis, bowel perforation, mesenteric ischemia
Pulmonary embolism	same
COPD/asthma	same
Hemorrhage	Non-traumatic hemorrhage, such as from a gastrointestinal, oropharyngeal or peripheral source
Anaphylaxis	same
Hypovolemia	Non-hemorrhagic, non-septic hypovolemia such as due to gastrointestinal losses

COPD = chronic obstructive pulmonary disease.

Table 2: Patient characteristics

Patient characteristics	Intervention n=94	Control n=85
Age, mean (years)	55.5	51.4
Male sex	47 (50.5%)	41 (48.2%)
Presenting signs and symptoms		
Systolic blood pressure <100mmHg	40 (42.6%)	32 (37.6%)
Heart rate >100 beats per minute	59 (62.8%)	55 (64.7%)
Respiratory rate >20 breaths per minute	75 (79.8%)	66 (77.6%)
SpO2 <92%	41 (43.6%)	30 (35.3%)
Glasgow Coma Scale ≤ 5	13 (13.8%)	13 (15.3%)
Dyspnea	71 (76.3%)	52 (61.2%)
Altered mental status	51 (54.3%)	55 (64.7%)
Diaphoresis	28 (29.8%)	31 (36.9%)
Intracranial mass effect	6 (6.5%)	8 (9.4%)
Arrhythmia	19 (20.4%)	14 (16.5%)

All percentages calculated without missing values. SpO2 = non-invasively measured oxyhemoglobin concentration.

Table 3: Ultrasound findings

n = 90 (%)	
Lung sliding	
Present	82 (91.1%)
Absent	6 (6.7%)
Inconclusive	2 (2.2%)
Lung point	
Yes	1 (1.1%)
No	89 (98.9%)
Lung profile	
A profile	39 (43%)
B profile	25 (27.8%)
Focal B profile	13 (14.4%)
Inconclusive	13 (14.4%)
Pleural fluid	
Yes	18 (20.0%)
No	71 (78.9%)
Inconclusive	1 (1.1%)
LV contractility	
Normodynamic	46 (51.1%)
Hypodynamic	17 (18.9%)
Hyperdynamic	26 (28.9%)
Inconclusive	1 (1.1%)
LV chamber size	
Normal	66 (73.3%)
Constricted	3 (3.3%)
Dilated	16 (17.8%)
Inconclusive	5 (5.6%)
RV strain	

Yes	4 (4.4%)
No	80 (88.9%)
Inconclusive	6 (6.7%)
IVC diameter	
Normal	53 (58.9%)
Flat	18 (20.0%)
Distended	16 (17.8%)
Inconclusive	3 (3.3%)
IVC collapsibility	
< 50%	58 (64.4%)
> 50%	27 (30.0%)
Inconclusive	5 (5.6%)
Intraabdominal fluid	
Yes	23 (25.6%)
No	56 (62.2%)
Inconclusive	11 (12.2%)
Pericardial fluid	
Yes	16 (17.8%)
No	71 (78.9%)
Inconclusive	3 (3.3%)
Aorta >3 cm	
Yes	6 (6.7%)
No	76 (84.4%)
Inconclusive	8 (8.9%)
Intimal flap/false lumen	
Yes	0 (0%)
No	82 (91.1%)
Inconclusive	8 (8.9%)
DVT	

Yes	3 (3.3%)
No	84 (93.3%)
Inconclusive	3 (3.3%)

LV = left ventricular, RV = right ventricular, IVC = inferior vena cava, DVT = deep venous thrombosis.

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Table 4: Final diagnostic syndrome

	n=180
Neurologic	50 (27.8%)
Sepsis	47 (26.1%)
Cardiac	24 (13.3%)
Endocrine	22 (12.2%)
Hepatic	7 (3.9%)
Renal	5 (2.8%)
Acute abdomen	4 (2.2%)
Pulmonary embolism	4 (2.2%)
COPD/asthma	3 (1.7%)
Hemorrhage	2 (1.1%)
Anaphylaxis	2 (1.1%)
Hypovolemia	1 (0.6%)
Other	3 (1.7%)
No diagnostic certainty	6 (3.3%)

COPD = chronic obstructive pulmonary disease.

Table 5: Diagnostic accuracy by for intervention and control groups

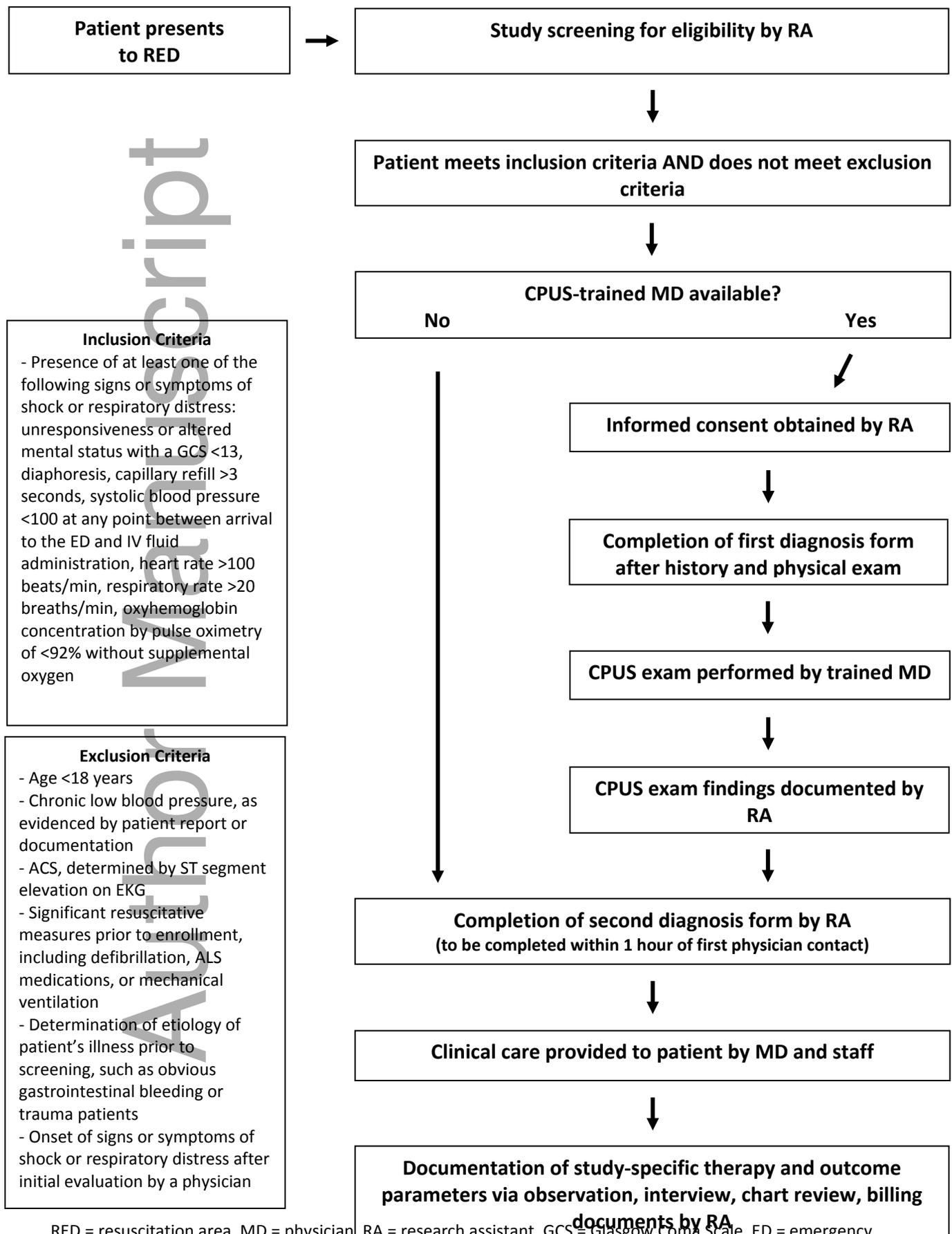
Correct initial diagnostic syndrome	Intervention n=89	Control n=84	Effect size (95% confidence interval)
Correct initial diagnostic syndrome (overall)	64 (71.9%)	48 (57.1%)	Δ 14.8% (0.5%, 28.4%)
Correct initial diagnostic syndrome by group (n, % correct of counts in this group)			
Neurologic	15 (68.2%)	19 (67.9%)	
Sepsis	19 (70.4%)	10 (50%)	
Cardiac	18 (94.7%)	2 (40%)	
Endocrine	4 (57.1%)	7 (50%)	
Hepatic	0 (0%)	3 (60%)	
Renal	0 (0%)	3 (100%)	
Acute abdomen	1 (50%)	0 (0%)	
Pulmonary embolism	3 (100%)	N/A	
COPD/asthma	N/A	1 (33.3%)	
Hemorrhage	1 (100%)	1 (100%)	
Anaphylaxis	2 (100%)	N/A	
Hypovolemia	N/A	0 (0%)	

Other	1 (50%)	2 (66.7%)
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“N/A” indicates that a particular diagnostic syndrome was not present in this group. “0” indicates that the diagnostic syndrome was present in the group, but no correct initial diagnoses were made. COPD = chronic obstructive pulmonary disease.

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Figure 1: Study workflow



RED = resuscitation area, MD = physician, RA = research assistant, GCS = Glasgow Coma Scale, ED = emergency department, IV = intravenous, min = minute, ACS = acute coronary syndrome, EKG = electrocardiogram, ALS = advanced life support, GI = gastrointestinal.

Figure 2: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram

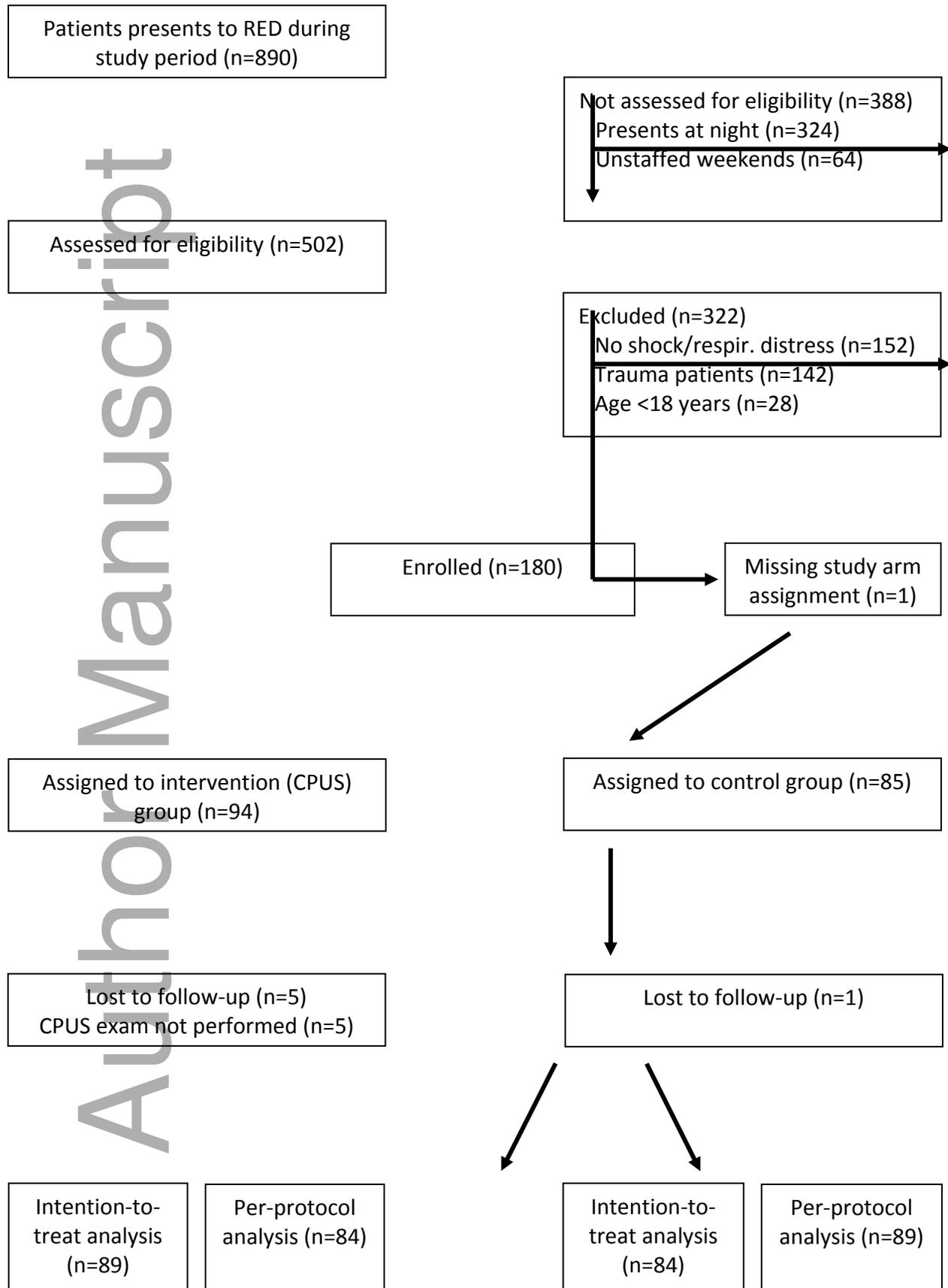
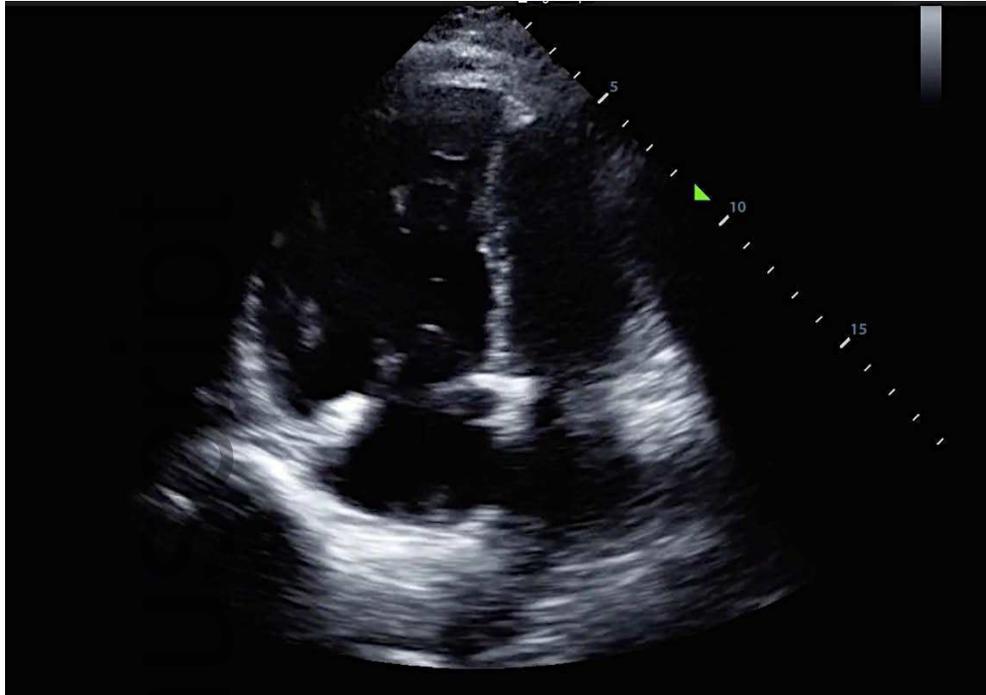


Figure 2: Examples of how ultrasound findings from the CPUS examination were used to help determine a leading diagnosis for patients with undifferentiated shock or respiratory distress.



A) Enlarged right ventricle imaged in apical four-chamber view. When seen with a distended, non-collapsing IVC in a patient with dyspnea, these findings are suggestive of a pulmonary embolism.



B) Free fluid in right upper quadrant. When seen with a hyperdynamic left ventricle and a flat IVC in a febrile patient with hypotension and abdominal pain, these findings are concerning for a sepsis, such as from typhoid fever.



C) B-lines imaged in bilateral lung fields. When seen with a hypodynamic left ventricle and a distended, non-collapsing IVC in a patient with hypotension and/or dyspnea, these findings are suggestive of decompensated systolic heart failure.



D) Pericardial effusion imaged in subxiphoid view. When seen with a distended, non-collapsing IVC in a patient with hypotension, these findings are concerning for cardiac tamponade.