Evaluating the Impact of Point-of-Care Ultrasonography on Patients with Suspected Acute Heart Failure or Chronic Obstructive Pulmonary Disease in the Emergency Department: A Prospective Observational Study

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Legend

ACEI	Angiotensin-Converting Enzyme Inhibitor
ACEP	American College of Emergency Physicians
ARB	Angiotensin II Receptor Antagonist
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CTAS	Canadian Triage and Acuity Scale
ED	Emergency Department
EF	Ejection Fraction
eFAST	Extended Focused Assessment with Sonography for Trauma
ESC	European Society of Cardiology
FAST	Focused Assessment with Sonography for Trauma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard Ratio
IQR	Interquartile Range
LAMA	Left Against Medical Advice
LV	Left Ventricular
LWBS	Left Without Being Seen
MI	Myocardial infarction
NOAC	Novel Oral Anticoagulant drug
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
OR	Odds Ratio
PDE4	Phosphodiesterase 4
PGY	Postgraduate Year
POCUS	Point-of-Care Ultrasonography
SD	Standard Deviation
SE	Standard Error
TIA	Transient Ischemic Attack
US	Ultrasonography

Abstract 1 (150 words)

Background: Acute heart failure and chronic obstructive pulmonary disease (COPD) exacerbation are common, and are sometimes difficult to differentiate in the emergency department (ED).

Objectives: To determine the clinical impact of Point-of-Care Ultrasonography (POCUS) in ED patients with suspected acute heart failure or COPD.

Methods: We conducted a prospective health records review with 1:3 matching, and analyzed time to events using time-dependent Cox regression analyses, classification performance, and adverse events.

Results: There were 81 patients with lung POCUS and 243 matched patients. No differences were found in ED length of stay or length of care, nor adverse events. Significance was found for time to treatment (P=0.02). Lung POCUS had high sensitivity (92.5%) and specificity (85.7%) for identifying acute heart failure.

Conclusions: Lung POCUS could result in faster treatments for patients with suspected acute heart failure and COPD, and has high accuracy in identifying acute heart failure.

Abstract 2

Background

Acute heart failure and exacerbation of chronic obstructive pulmonary disease (COPD) are common causes of shortness of breath, and are sometimes difficult to differentiate in the emergency department (ED).

Objectives

We sought to determine the clinical impact of Point-of-Care Ultrasonography (POCUS) in ED patients with suspected acute heart failure or COPD. Our primary outcome was the impact of lung POCUS on ED length of stay. Secondary outcomes were: 1) length of patient care by physicians in the ED, and 2) time to appropriate treatment; 3) classification performance of lung POCUS; and 4) incidence of pre-defined adverse events.

Methods

A prospective health records review with 1:3 frequency matching at The Ottawa Hospital between March-September, 2017 was used. We included patients aged 50 and older with shortness of breath or cough from suspected acute heart failure or COPD. We analyzed 1) time to events using Cox regression analyses with a time-dependent variable; 2) classification performance with 95% confidence intervals (CI); and 3) incidence of adverse events using multivariable logistic regression analyses.

Results

There were 81 patients evaluated with lung POCUS and 243 matched patients. Lung POCUS did not impact ED length of stay (adjusted hazard ratio [HR], 1.11 [95% CI, 0.85-1.46], P=0.44) or ED length of care (adjusted HR, 1.05 [95% CI, 0.79-1.40], P=0.73). That said, patients evaluated with lung POCUS received disease-specific treatment faster

(adjusted HR, 1.50 [95% CI, 1.05-2.15], P=0.03). ED physicians correctly identified acute heart failure with lung POCUS with a sensitivity of 92.5% (95% CI, 83.4-97.5%) and specificity of 85.7% (95% CI, 57.2-98.2%). We found no differences in incidence of adverse events.

Conclusions

Lung POCUS has high sensitivity and specificity in identifying acute heart failure, and could potentially result in faster administration of disease-specific treatments for patients with suspected acute heart failure and COPD.

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Chapter 1. INTRODUCTION

Acute heart failure and exacerbations of chronic obstructive pulmonary disease (COPD) are common causes of shortness of breath, and are often not easy to differentiate in the emergency department (ED).[1,2,3] Heart failure and COPD are the leading conditions for which patients are admitted from EDs in Canada.[4]

1.1. Acute Heart Failure in the ED

Acute heart failure refers to the rapid onset or deterioration of symptoms and/or signs of heart failure, which is defined as a *"complex clinical syndrome such as shortness of breath, ankle swelling and fatigue that results from any structural or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress,"* according to the American and European guidelines for heart failure.[5,6] Heart failure is a disease seen all over the world and is commonly seen in the ED. There are approximately 26 million patients with heart failure worldwide.[7] In Canada, an estimated 600,000 people live with heart failure with increasing hospital visits for the past several years.[8] In the United States, 6.5 million over 20 years of age are estimated to have heart failure, and there are 960,000 new heart failure cases diagnosed annually.[9] Heart failure often causes pulmonary edema, which is an excessive accumulation of pulmonary extravascular water as a consequence of increased hydrostatic pressure in pulmonary capillaries. Pulmonary edema secondary to heart failure is the main cause of acute respiratory failure in elderly patients.[3]

Heart failure can result from any structural or functional ventricular dysfunction that impairs cardiac output. Cardiac problems such as valvular heart disease, ischemic disease, or arrhythmia, can lead to cardiac pump failure and are common in patients in heart failure.

However, non-cardiac conditions such as anemia, pulmonary, renal, or hepatic disease can also contribute the exacerbation of heart failure symptoms through increased vascular resistance, oncotic imbalance, fluid retention, and so forth. Fluid accumulation within the pulmonary interstitial and/or alveolar spaces develops pulmonary edema, which commonly causes shortness of breath in patients with acute heart failure.

ED physicians have to treat patients with acute heart failure without delay, since early treatment is associated with improved clinical outcomes.[10] Oxygen therapy and ventilator support, including non-invasive positive pressure ventilation are essential for patients with respiratory distress. Patients may need inotropic agents if they are in cardiogenic shock, or other specific treatment depending on underlying causes (e.g. coronary revascularization for concomitant myocardial infarction, renal replacement therapy for refractory volume overload).[5,6] Intravenous diuretics and intravenous vasodilators, if not contraindicated, are the initial specific treatments for patients with significant pulmonary congestion.

Although there are American and European guidelines for diagnosis, the diagnosis of acute heart failure in the ED is not simple. If patients with a prior cardiovascular history display typical signs and symptoms, such as bilateral rales and paroxysmal nocturnal dyspnea, it is easy for ED physicians to diagnose and treat acute heart failure. If not, diagnosis and administration of appropriate treatment takes a longer time; in order to gather enough information to diagnose. There are several recommended diagnostic tools to assess acute heart failure according to the guidelines. Chest X-ray can be a useful test to evaluate cardiomegaly, pleural effusion, and pulmonary congestion. However, a normal chest X-ray does not always exclude congestive heart failure due to the limited sensitivity.[11] Early

echocardiography to assess cardiac function should also be performed if available, since it is considered as the most useful test in patients with suspected heart failure for the diagnosis.[6] Measurement of serum B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is recommended by both the American and European guidelines for clinical diagnosis of acute heart failure. However, measurement of BNP may result in treatment delay for acute heart failure, which may cause increased mortality.[12] Furthermore, gray zone BNP levels (100 - 400 pg/ml) may not be helpful as a diagnostic test for acute heart failure.[13] Further research is required to improve management of acute heart failure in the ED.

1.2. COPD Exacerbation in the ED

COPD is a common disease characterized by *"persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases,"* as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[14] It is a common disease worldwide and frequently seen in the ED as acute exacerbations. There are approximately 174 million COPD patients worldwide according to the Global Burden of Disease Study in 2015.[15] In Canada, 772,200 people are estimated to be living with COPD.[16]

The GOLD suggests that any patients with shortness of breath, chronic cough, or sputum production with/without risk factors such as smoking should be considered to have COPD. Although cigarette smoking is the most well-studied COPD risk factor, it is important to consider COPD for non-smoking patients with these symptoms as well, because a substantial proportion of patients with COPD have never smoked.[17,18] While COPD is a chronic condition, patients with COPD present to the ED with shortness of breath or cough

due to exacerbations usually associated with increased airway inflammation, sputum production, and/or air trapping. The management of COPD exacerbation should be based on an assessment of signs and symptoms.[14] The symptoms may be treated with inhaled bronchodilators, systemic corticosteroids, and/or antibiotics depending on patients' condition in the ED.[19] Oxygen therapy and ventilator support including non-invasive mechanical ventilation may be required for patients with severe exacerbation.

1.3. Difficulty in Differentiation

The ED diagnosis of acute heart failure or COPD exacerbation is usually based on clinical suspicion using the patient's history, symptoms (e.g. shortness of breath, cough, and/or sputum production), physical examination, laboratory studies, and/or radiological images. It may be difficult to differentiate acute COPD exacerbation from acute heart failure since the clinical information is not specific to one condition or the other, and there is no standardized clinical criteria to diagnose and differentiate these diseases in the ED.[20,21]

Severely ill patients may have more overt signs and symptoms, therefore, they could be diagnosed quickly, and aggressive supportive respiratory management is essential for life-saving. On the other hand, patients with relatively mild signs and symptoms may be more difficult to differentiate and take longer to diagnose in the ED, especially when they have overlapping risk factors for both heart failure and COPD without clear history of exacerbations.

Moreover, COPD is commonly underdiagnosed.[22] Patients with multiple risk factors who have not completed a full assessment for the diagnosis of COPD may visit the ED with shortness of breath and a known cardiac dysfunction. These patients may be more difficult to differentiate COPD exacerbation from acute heart failure than those who have history of

multiple exacerbations with known decreased pulmonary function and no known cardiac problem.

Beyond the history and physical examination, a complete assessment including laboratory results often takes more than 40 minutes and sometimes longer depending on the availability of laboratory services.[23,24] Obtaining chest X-ray might take even longer depending on ED crowding and the availability of radiography services. These tests may delay the initial diagnosis and increase ED length of stay. A final diagnosis, especially for the first presentation, requires confirmatory tests of cardiac function for heart failure, and spirometry for COPD, which often only occur after admission to a hospital. Initial ED management has to be provided quickly, without laboratory and/or chest X-ray or other confirmatory tests. As a result, patients are often treated for both heart failure and COPD, and then re-evaluated to assess initial treatment responses.[2]

1.4. ED Length of Stay and ED Crowding

Patients in the ED should be assessed in a timely manner and treated with minimal delay. ED length of stay is a key indicator of the efficiency of patient care in the ED; longer length of stay can lead to ED crowding.[25] ED crowding is defined as the following by the American College of Emergency Physicians (ACEP) Crowding Resources Task Force: "*A situation in which the identified need for emergency services outstrips available resources in the ED. This situation occurs in hospital EDs when there are more patients than staffed ED treatment beds and wait times exceed a reasonable period. Crowding typically involves patients being monitored in non-treatment areas (eg, hallways) awaiting ED treatment beds or inpatient beds. Crowding may also involve an inability to appropriately triage patients, with large numbers of patients in the ED waiting area of any triage assessment category.*"[26]

ED crowding is a major concern of health care systems for many countries, including Canada.[27] Previous literature suggests that ED crowding is associated with adverse clinical outcomes including treatment delay, medical errors, and mortality.[28] Early treatment in the ED can improve clinical outcomes and relieve symptoms early, both of which are important to patients.

Yoon and colleagues conducted a retrospective review to identify factors associated with ED length of stay. They showed that triage levels, diagnostic investigations, and consultations were independent predictors of ED length of stay.[29] Casalino and colleagues conducted a prospective study to evaluate predictive factors for longer ED length of stay. They found that ED length of stay was associated with patients' acuity and complexity, as well as the need for diagnostic and therapeutic interventions.[30] Since patients who are suspected of acute heart failure or COPD exacerbation tend to have multiple comorbidities and often need diagnostic and therapeutic interventions, these population may have longer ED length of stay, which may contribute to ED crowding. It may be possible to decrease ED length of stay if ED physicians can make diagnoses and treat patients faster, and reduce unnecessary interventions for patients.

1.5. POCUS in the ED

Bedside ultrasonography (US), or point-of-care US (POCUS), is described in the ACEP policy statement as *"the medical use of US technology for the bedside evaluation of acute or critical medical conditions."*[31] Its use has been increasing in the ED since its introduction in the 1980s and is now widely adopted; including in Canada.[32,33,34]

Learning how to perform focused assessment with sonography for trauma (FAST) examination (to look for free fluid suggesting bleeding in the peritoneal, pericardial, and

pleural cavities), and extended FAST (eFAST; incorporating basic thoracic assessment for pneumothorax), is mandatory in most emergency medicine residency training programs in Canada and the United States. However, the use of lung POCUS to differentiate acute heart failure from COPD exacerbation seems to be less prevalent.[35,36] Lung POCUS is the bedside evaluation of the lungs using an US probe on the chest walls. Lung POCUS can identify acute heart failure and lung congestion by the presence and the number of B-lines, which are sonographic artifacts through the chest.

1.6. Accuracy of Lung POCUS for Acute Heart Failure

Accuracy is an essential feature in any and all types of diagnostic tests. A recent systematic review to determine the ability of lung POCUS to diagnose heart failure showed that it had a sensitivity of 94.1% (95% confidence interval (CI), 81.3% to 98.3%) and a specificity of 92.4% (95% CI, 84.2% to 96.4%).[37] Another systematic review showed that the sensitivity of lung POCUS in the ED was 85.3% (95% CI, 82.8% to 87.5%) and the specificity was 92.7% (95% CI, 90.9% to 94.3%). Chest radiographic findings of pulmonary edema had a sensitivity of 56.9% (95% CI, 54.7% to 59.1%) and a specificity of 89.2% (95% CI, 87.9% to 90.4%).[38] In both reviews, the reference standard for a final diagnosis of acute heart failure was a diagnosis reached by physicians after a retrospective review of inpatient medical records.

An Italian prospective observational study investigated the diagnostic impact of implementation of lung POCUS to diagnose acute heart failure on patients with shortness of breath due to suspected acute heart failure in the ED. After excluding those already invasively ventilated (i.e. mechanically ventilated through an endotracheal tube or a tracheostomy tube) at the time of evaluation, they showed that performing lung POCUS in

addition to initial clinical assessment achieved a significantly higher accuracy in differentiating acute heart failure from non-cardiac causes of acute shortness of breath than the initial clinical workup, chest radiograph, and serum BNP.[39] Another recent study suggested that a combination of chest radiography, lung POCUS, and NT-proBNP assay could be a reasonable approach to diagnose acute heart failure accurately in patients with shortness of breath in the ED.[40]

Although lung POCUS is suggested in the European guidelines for diagnosis and treatment of heart failure for additional diagnostic information if expertise is available, it is not currently considered standard care for acute heart failure.[41] This is possibly because diagnostic accuracy with standard management (without lung POCUS) is thought to be sufficient. As such, ED physicians may feel there is little information to be added in many cases, or that it is a time-consuming procedure. ED physicians may need more knowledge translation strategies to incorporate new procedures, and other barriers such as a training opportunity and machine availability in the ED may need to be addressed.[42]

1.7. Learning Lung POCUS for Acute Heart Failure

Lung POCUS is remarkably easy to learn. Previous literature show that learning lung POCUS was easy for even non-physicians to be able to assess accurately.[43,44] Chiem and colleagues demonstrated that newly-trained sonographers could perform lung POCUS for acute heart failure with similar accuracy to expert sonographers.[45]

1.8. Saving Time with POCUS

There are several articles describing time reduction using POCUS, including POCUS in pediatrics, abdominal POCUS, POCUS for deep vein thrombosis, and pelvic POCUS that could decrease ED length of stay.[46,47,48,49] Hall and colleagues reported that POCUS for

nontraumatic shock improved time to admission request when performed early for ED patients with shock.[50] Reed and colleagues reported a non-significant trend of improvement in time to diagnosis, favoring POCUS for ruptured abdominal aortic aneurysm where the median times of diagnosis were 60 minutes in the POCUS group, and 111 minutes in the no POCUS group (P=0.09).[51] However, the time effectiveness of lung POCUS in a real clinical setting has not yet been reported.

1.9. Quality Improvement in Patient Care

Withholding treatment may result in negative consequences. Ray and colleagues conducted a prospective observational study in France and analyzed admitted patients 65 years of age or more with acute respiratory symptoms. They assessed the ED diagnoses and treatment of cardiogenic pulmonary edema, pulmonary embolism, pneumonia, and acute asthma before thoracic computed tomography scan, Doppler echocardiography, or pulmonary function tests were performed. They concluded that withholding appropriate treatment in the ED may lead to higher mortality (adjusted odds ratio (OR), 2.83 [95%CI, 1.48 to 5.41] P=0.002) in elderly patients with acute respiratory failure.[3]

Potentially, because it can be challenging to differentiate between the two conditions, patients who are misdiagnosed might receive unnecessary treatment, such as bronchodilators for patients with acute heart failure or diuretics for patients with COPD exacerbation. Despite being careful about investigating the etiology of shortness of breath, ED physicians may nevertheless end up administrating unnecessary treatments to patients.

Wuerz and colleagues conducted a retrospective study on early heart failure treatment in prehospital settings. They found higher mortality in those who were mistakenly diagnosed with congestive heart failure (i.e. patients had different conditions such as

pulmonary diseases) and administered heart failure treatment (e.g. nitroglycerin, furosemide, and/or morphine sulfate), compared to those who were correctly treated (13.6% vs. 3.8% respectively; $P<0.05$).[52] Singer and colleagues conducted a retrospective analysis of a multi-centre patient registry of acute decompensated heart failure. They found that those with acute heart failure and no history of COPD who received inhaled bronchodilators by the emergency medical services or in the ED had a greater need for aggressive interventions and monitoring than those who did not receive bronchodilators.[53]

According to these studies, administering both treatment for heart failure and COPD, or administering inappropriate treatment to patients with heart failure or COPD may not only be a financial burden, but may also be potentially harmful to patients. Quality improvement in healthcare is essential. Lung POCUS might potentially reduce these adverse events since it has high diagnostic accuracy and can be performed quickly.

1.10. Thesis Rationale

Acute heart failure and COPD patients are common in the ED, and present with similar respiratory symptoms. These conditions are sometimes not easy to differentiate in the ED, and may be associated with the prolonged time to diagnosis or disposition, and possibly ED length of stay. There is also an increased risk of unnecessary treatment, which is not only a waste of medical resources, but could also be potentially harmful to patients. Because lung POCUS for the assessment of pulmonary edema is an accurate, easy, and relatively quick examination in the ED, it could reduce the time to diagnosis and improve the quality of care in the ED. However, it is currently not the standard of care for patients with shortness of breath; use of lung POCUS is up to individual ED physicians.

Several studies have confirmed the accuracy of lung POCUS and its efficiency; it can usually be completed in three to five minutes, which is shorter than any other imaging tests to help with decision-making. However, there is a paucity of research on any potential effects of the use of lung POCUS on patient-oriented outcomes.

Chapter 2. OBJECTIVES

The overall objective of this thesis is to determine the clinical impact of lung POCUS on patient-oriented outcomes, which are relevant to patients, ED physicians, and administrators, in a real clinical setting. Given that many studies have already emphasized the accuracy of lung POCUS in diagnosing acute heart failure, we chose to focus on ED length of stay (i.e. the total time spent in the ED), since it is one of the important patient-oriented outcomes.

We also aimed to assess the ED length of care, which is the total length of patient care by physicians in the ED; since ED length of stay is directly associated with ED crowding and hospital bed availability, which cannot be controlled by physicians.[54,55] In order to minimize the effects of these factors, it is defined as the interval of time from physician initial assessment to disposition decision of discharge or admission. Although we know that ED physicians do not make admission decisions for patients who need to admit to a hospital, the time of admission decision is more important from the patient's perspective than the time of consultation to other departments by ED physicians; for when admission decisions are made, patients can theoretically move to hospital beds.

Additionally, we chose the time to appropriate disease-specific treatment administration time as a patient-oriented outcome because the faster administration of appropriate treatment can releave patient's symptoms faster, therefore this is also important for patients.

As lung POCUS is accurate and requires less time than any other imaging tests for diagnosis of acute heart failure in the ED, it can be most beneficial if it is performed in the

early stage of patient care. As such, we will determine the clinical impact of lung POCUS on time reduction and diagnostic accuracy in the ED.

The specific objectives of this thesis are as follows:

Primary Objective

1. To determine the impact of using lung POCUS compared to standard management without lung POCUS on ED length of stay among patients with shortness of breath secondary to suspected acute heart failure or exacerbation of COPD.

Secondary Objectives

2. To determine the impact of using lung POCUS compared to standard management without lung POCUS on ED length of care by physicians in the ED among patients with shortness of breath secondary to suspected acute heart failure or exacerbation of COPD.
3. To determine the impact of using lung POCUS compared to standard management without lung POCUS on time to disease-specific treatment administration in the ED among patients diagnosed with acute heart failure or exacerbation of COPD.
4. To determine the classification performance of lung POCUS and its ability to recognize acute heart failure compared to both chest X-ray and final diagnosis of acute heart failure and/or COPD.
5. To determine the impact of the use of lung POCUS on the incidence of adverse events such as potentially unnecessary treatment administration, return ED visits within 7 days after the initial ED visit, and inappropriate ED diagnosis compared to standard management without lung POCUS.

Chapter 3. METHODS

3.1. Study Design

We performed a prospective health records review comparing matched cohorts of patients who were and were not exposed to Lung POCUS. We performed 1:3 frequency matching to improve statistical power.

3.2. Study Setting

The study was conducted at The Ottawa Hospital, General and Civic campuses, which are university-affiliated, comprehensive tertiary care facilities in Ottawa, Ontario, Canada. The University of Ottawa Heart Institute is physically attached to the Civic campus. Patients seen in the ED are usually self-referred. However, they can also be sent by other physicians. The ED serves a primarily adult population with a volume of more than 172,000 patients annually at the two campuses of The Ottawa Hospital. The ED staff are all full-time and certified in emergency medicine and have all completed either a specialty program in emergency medicine accredited by the College of Family Physicians of Canada or the Royal College of Physicians and Surgeons of Canada. Resident physicians in both programs are also working in the ED.

POCUS for Emergency Medicine has been practiced at The Ottawa Hospital since 1998. POCUS has been a core competency of Emergency Medicine specialty training since 2008. The Emergency Medicine Ultrasonography team has been delivering practical training of POCUS to all the residents and ED staff since 2003. In addition, Residents and staff physicians may be credentialed for lung POCUS after completing a combination of existing on-line material, image review cases, and supervised scanning. Trainees receive group instruction including 30-minute demonstrations and recording scans over a period of four to

six weeks. Growing numbers of staff are credentialed in the use of lung POCUS. Approximately 70% of the ED staff are already credentialed for core POCUS skill, including lung POCUS, at The Ottawa Hospital.

There are also a few non-physician sonographers in the Emergency Medicine Ultrasonography team, who are POCUS credentialed medical students and POCUS credentialed ultrasound technicians. They help ED physicians perform lung POCUS, record the clips, and document the interpretation of the findings under supervision by the Emergency Medicine Ultrasonography team. Medical students, residents, and staff in the ED who are credentialed can be asked to perform POCUS as per the request of the most responsible physician. The most responsible physician may or may not be credentialed, but can request that POCUS be performed and use the results of the POCUS of the patient accordingly. The most responsible physician also has the option of performing lung POCUS themselves and use this information to manage patients. All of this is usual care in the ED at our institution.

The ED has three US machines at each campus. There are two Zonare Z.one (Mountain View, CA) machine with curvilinear, linear, phased array, and endocavitary transducers, as well as one GE Logiq E (Waukesha,WI) machine with curvilinear, linear, phased array, and endocavitary transducers at each site. All POCUS images and findings are archived by sonographers in the Qpath software by Telexy (Maple Ridge, BC) regardless of the modality. All POCUS scans archived to Qpath undergo quality improvement and are reviewed by the Emergency Medicine Ultrasonography team to confirm findings.

The Ottawa Hospital uses an electronic health record system called Oacis developed by Dinmar (Ottawa, ON). All the other health records are available through Oacis.

3.3. Population

All patients who were assessed by ED physicians at The Ottawa Hospital for shortness of breath or cough secondary to suspected acute heart failure or COPD, for a six-month period starting on March 16th in 2017, were eligible for this prospective health records review. We included patients who were 50 years of age or older and had suspected diagnoses of acute heart failure or COPD by ED physicians. We included patients who were 50 years or older since heart failure and COPD as a cause of shortness of breath or cough are not prevalent in a younger population.[20,21] The cut-off age of 50 is used to define the population for the Ottawa Heart Failure Risk Scale as well.[56] We considered documented ED diagnoses in physician records, regardless of the uncertainty of the diagnoses (e.g. diagnosis with a question mark), as suspected diagnoses in the ED; since ED physicians have to document the most likely diagnosis at the time in the medical record as a current diagnosis. We used diagnostic criteria by the European Society of Cardiology (ESC) for acute heart failure for the final diagnosis.[6] For lung POCUS, we only included the recorded lung POCUS with a clinical indication to Qpath. Scans with an educational purpose were not included since they would not affect any clinical decision making in the ED.

We excluded patients diagnosed with acute ST-segment elevation myocardial infarction on arrival electrocardiogram since they require a very different management. We also excluded those who had known history of interstitial fibrosis, extensive lung cancer, pneumonectomy or lobectomy, or pneumothorax since lung POCUS can provide only limited findings to diagnose heart failure in these patients. We did not exclude dialysis dependent patients because physicians can still perform lung POCUS in order to assess

pulmonary edema, and COPD is a frequent and underdiagnosed comorbidity in these patients.[57]

This study was approved by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) on March 16th, 2017 (Protocol Number: 20160893-01H). It was conducted under a waiver of informed consent because (1) patients were not being intervened upon: POCUS is already part of the current clinical practice, and routine care of patients was not altered for the research; and (2) no identifiable private information was collected from patients for the research.

3.4. Identification of Patients for Analysis

For this study, we identified patients for analysis through the following strategy:

Step 1. Identification of patients with suspected diagnosis of acute heart failure or COPD

a. We first identified potentially eligible patients (50 years of age or older with a presenting complaint of "shortness of breath" or "cough") by reviewing administrative lists of patients who visited the ED within the study period;

To complete Step 1a, we received lists of patients with visits to the ED from the hospital administration service on a daily basis. It contained patient ID and patient characteristics including visit date, visit time, age, sex, presenting complaint, and electronically stamped time information. From this list, we selected the eligible patients who were 50 years of age or older, and who had a presenting complaint of "shortness of breath" or "cough".

b. For all potentially eligible patients, we accessed their health records through Oacis to confirm the suspected diagnosis in the ED;

For Step 1b, we used the patient medical record numbers to access the electronic health records in Oacis to identify suspected diagnoses. The suspected diagnoses in the ED were confirmed if they were documented in the ED physician's chart.

Step 2. Identification of exposure to lung POCUS

a. We manually reviewed all ED records of POCUS in Qpath, where lung POCUS clips and findings are archived, to identify any patients with lung POCUS;

Step 3. We merged the two lists above by using unique medical record numbers to identify the subset of eligible patients who were exposed to lung POCUS; all remaining patients were classified as not exposed to lung POCUS.

3.5. Matching Procedure

For each patient with lung POCUS, we purposely selected a (non-random) consecutive sample of 3 patients without lung POCUS using the following three matching criteria: five-year age strata, same sex, and with or without a previous diagnosis of heart failure and/or COPD (i.e. patients with history of heart failure but no history of COPD, history of COPD but no heart failure, history of heart failure and COPD, and no history of heart failure or COPD). We chose these three matching criteria because they are potential confounders, and because previous diagnosis of heart failure and/or COPD may affect physicians' decision making to perform lung POCUS given the diagnostic challenges and perceived usefulness of lung POCUS among these groups.[2,58,59,60] We included patients with no prior documented history of heart failure or COPD because some of them may have the disease but were not diagnosed due to limited assessment.

3.6. POCUS Protocol

During the study period, ED physicians evaluated all patients in their usual clinical practice without any additional interventions. ED physicians were not aware of the existence of our study and did not have to fill any study form or documentation beyond their usual practice.

Although the Emergency Medicine Ultrasonography team in the ED provides practical training for POCUS for all the residents and ED staff, credentialed physicians may not be available all the time. There were also trained medical students as sonographers available in the ED during this study period to help ED physicians for the lung POCUS assessment, archiving, and documentating to Qpath. They were volunteering only during summer time, from May 1st to August 31st, 2017.

For lung POCUS, we use an 8-zone technique where the chest is divided into 4 zones on each side for assessing pulmonary edema as described by Volpicelli et al.[61,62] Pulmonary edema is considered to be present (POCUS positive) if sonographic signs of pulmonary edema are present in more than two zones per side. The sonographic sign for pulmonary edema is a vertical artifact called B-line, which is generated by multiple reflections of the ultrasound beam trapped between the edematous lung interlobular septa. Each scan is deemed to be positive when at least three B-lines with a distance between adjacent lines of no more than 7 mm are identified.[58,61] A Zonare machine or a GE machine with a phased array 3.5-MHz probe is used for lung POCUS. A few examples of B-lines on lung POCUS are presented in Appendix A.

For the heart assessment, a right parasternal view is used to evaluate the left ventricular (LV) ejection fraction (EF), and evaluated visually by wall contraction and

thickening. LV function is further classified as Normal/Mild dysfunction (EF = 40 – 70%); Moderate/Severe dysfunction (EF < 40%); or Hyperdynamic (EF > 70%).[63] We collected this information when LV EF was evaluated along with lung POCUS.

Sonographers were responsible for documenting their own assessments in Qpath where there was the assessment format for the findings, as well as archiving the clips and images. The procedures above are all performed as a usual medical practice by ED physicians.

3.7. POCUS Interpretation

Standard practice includes POCUS interpretation made by the credentialed provider, and documented in the electronic archiving database (Qpath) and/or the record of treatment. The Emergency Medicine Ultrasonography team routinely reviews all archived images within Qpath as part of the quality assurance program. The examination was considered inconclusive when image quality was low or data were missing.

When the image was archived, no interpretations were made in either the Qpath record or the physician's chart, two investigators (SN and MW) interpreted the POCUS findings without other clinical findings.

3.8. The Reference Standard for the Final Diagnosis

The reference standard for the final diagnosis of acute heart failure or COPD was defined as per best available information. We used the following hierarchy of criteria to define the reference standard:

1. A discharge diagnosis for admitted patients,
2. An ED diagnosis with a repeat ED visit or a follow-up visit to outpatient clinic for the same initially presumed diagnosis within a month after the first ED visit, or

3. In all other cases where only a diagnosis made by ED physician was available for patients seen once in the ED and discharged home following treatment, study investigators reviewed health records of the ED care independently and determined the final diagnosis by consensus.

For the ED diagnosis with a repeat ED visit or a follow-up visit to outpatient clinic (the second criteria above), we assessed the medical records by following visits to the department of cardiology, internal medicine, general medicine, or outpatient clinic outside of The Ottawa Hospital if the documents were scanned into the electronic medical record at The Ottawa Hospital. The determination of the final diagnosis was made if there was documented agreement with the ED assessment of acute heart failure or COPD. If there was no agreement or documentation, the final diagnosis was made by health records review.

The health records review in the third criteria above was conducted using the following criteria: new or acute worsening of shortness of breath and other respiratory symptoms such as cough or fatigue, or clinical signs of pulmonary fluid retention to be suspected, laboratory data, and documented response to the ED treatments, as well as radiology reports of chest radiography, and sonographic reports of cardiology-performed or radiology-performed echocardiography if available. The health records review was performed only using the information from the health records in Oacis, and the reviewers were blinded to the archived POCUS images and the sonographers' interpretations in Qpath. However, if there was documentation of POCUS findings and/or interpretations in the ED health records in Oacis, the reviewers were not blinded to it. The determination of the final diagnosis was reached by consistency with ED diagnosis or consensus among two investigators.

3.9. Outcome Measures

3.9.1. Primary Objective (Objective 1)

For our primary objective of evaluating the impact of POCUS on ED length of stay, we obtained the time of registration, which is the time when the patient presents for services to the ED and is officially registered as a patient, and the time the patient left the ED, which is the moment of the admission or the time when the patient physically leaves the ED regardless of destination, including discharge home or transfer to another institution. ED length of stay was defined as the interval between these times. The time of POCUS was defined using the automatically recorded time when the first lung image for assessing B-lines was archived in Qpath. If patients died in the ED, the time of death was also recorded.

3.9.2. Secondary Objectives (Objective 2)

For our secondary objective of evaluating the impact of POCUS on the length of patient care by physicians in the ED, or ED length of care, we obtained the time of physician initial assessment, which is electronically time-stamped when ED physicians pick up a patient's chart and assign themselves to their care, and the time of disposition, which is electronically time-stamped when ED physicians or consulted physicians by ED physicians make the decision about the patient's disposition, such as to discharge, transfer, or admit the patient. ED length of care was defined as the interval between these times. This time interval was the length of patient care in the ED by any physicians including consulted physicians. As such, it did not include the wait time from registration to physician initial assessment time, nor the wait time from disposition decision time to the time the patient left ED; which may have been the wait time for hospital beds if patients were admitted.

3.9.3. Secondary objectives (Objective 3)

For our third objective of evaluating the impact of POCUS on time to disease-specific treatment administration in the ED, we classified all patients based on whether or not they were administered disease-specific treatment in the ED. Patients were classified as receiving appropriate treatment when the final diagnoses in the ED were matched with the disease-specific treatment. All remaining patients were classified as not having received appropriate treatment. We defined time to disease-specific treatment administration as the time interval between the time of physician initial assessment and the time of disease-specific appropriate treatment administration (i.e. the time of medication given by a registered nurse). Disease-specific treatment for acute heart failure was defined as diuretic administration, intravenous vasodilator administration, or emergency dialysis as they are the main agents that relieve shortness of breath due to pulmonary congestion. Disease-specific treatment for COPD exacerbation was defined as administration of bronchodilator such as beta-agonist or anticholinergic, or inhaled or systemic (oral or intravenous) steroid administration since they are the main agents to relieve shortness of breath for COPD. Oxygen therapy and ventilator support such as non-invasive mechanical ventilation were not considered as disease-specific treatment because they would be considered for both patients.

3.9.4. Secondary objectives (Objective 4)

For our fourth objective of evaluating classification performance of lung POCUS, we assessed sensitivity, specificity, positive predictive value and negative predictive value for identifying acute heart failure by the reference standard diagnosis. We also assessed the physician's ED impression based on all the information they received in the ED, which were obtained from the ED physicians' chart documentation. We compared these diagnostic

characteristics with the reference standard diagnosis between two groups: those with lung POCUS and those without lung POCUS. We evaluated inter-observer agreement by comparing image interpretations between ED physicians initially producing the images and the Emergency Medicine Ultrasonography quality assurance team reviewing them.

3.9.5. Secondary objective (Objective 5)

For our fifth objective of evaluating the impact of lung POCUS on the incidence of adverse events, we defined adverse events as i) potentially unnecessary treatment administration, ii) return ED visits within 7 days after initial ED visit, and iii) inappropriate diagnosis in the ED. The potentially unnecessary treatment administration was defined as the disease-specific treatment administered in the ED inconsistent with the reference standard diagnosis (e.g. heart failure-specific treatment administration to those without heart failure, or COPD-specific treatment administration to those without COPD). We also recorded for each patient whether or not they returned to the ED with a related respiratory complaint within 7 days after the initial visit. We compared the physician's ED impression in the ED with the reference standard diagnosis for the assessment of inappropriate diagnosis. The inappropriate diagnosis was defined as ED diagnosis inconsistent with the final diagnosis by the reference standard. We followed up our patient visit log for return visits within 7 days to The Ottawa Hospital.

3.10. Data Collection

We developed and pilot-tested a standardized data collection tool a priori to facilitate the extraction of data from existing records. The data collection tool is presented in Appendix B. We collected information on patient demographics and results of investigations from triage notes, ED health records by ED physicians, nursing documentation, and

radiological reports. Information on treatment received was obtained from ED records of treatment and nursing documentation.

Information on various times was obtained from triage notes, ED records of treatment, nursing documentation, POCUS archive image records, and administrative records. The time of registration, triage, physician initial assessment, disposition decision and patient left ED are time-stamped in the health record and the information was digitally provided from hospital administration service during the study period. The time of disease-specific treatment is hand-written in the nursing documentation.

For the final diagnosis, we reviewed discharge summaries for admitted patients as well as the health records after the initial ED visits to assess the appropriate treatment, diagnostic accuracy of lung POCUS, and the incidence of adverse events.

For the presence or absence of past history, current medications, clinical symptoms, and physical findings, we considered no documentation in the health records as absence because we assumed it was not observed if it was not documented. We relied on good documentation practices in the ED. If there was no documentation of the continuous variables such as blood pressure, heart rate, body temperature, and respiration rate in the health records, we considered these as missing data. A single investigator routinely completed the data collection tool, including initial findings of performed POCUS from electronically archived medical records documented by physicians and nurses.

3.11. Data Management

This study database was first created in Microsoft Excel (Redmond, WA). It was imported to a statistical software, SAS 9.4 (Cary, NC), for analyses.

We used a standardized Excel spreadsheet for the entry of the data extracted from routinely collected sources. We received the list of patients with ED visits every day, provided by the hospital administration service, which contained patient hospital ID and patient characteristics. We electronically transferred it into the main database, which were archived in the encrypted computer at The Ottawa Hospital. The patient ID for the hospital was recorded in a separate Excel spread sheet for privacy assurance. All the data entry was performed by one person (SN).

Data cleaning was done using Microsoft Excel by running filters and looking for outliers as well as using logic checks. SAS software was used to identify illogical, unacceptable, or missing data with frequency reports.

3.12. Statistical Analyses

SAS software was used for all statistical analyses. For data exploration, we used visual inspection of the data through frequency tables and graphical exploration of distributions with box plots and histograms.

3.12.1. Descriptive Analyses

Patient clinical and demographic characteristics at baseline were described using means and standard deviations for continuous variables, or medians and inter-quartile ranges if skewed, and frequencies and proportions for categorical variables. Patient characteristics were compared between those with and without lung POCUS using Student's t-test for the comparison of two means, Mann-Whitney U test for continuous variables not normally distributed, and Fisher’s exact test for categorical variables.

Lung POCUS interpretations based on the review by investigators were described using a frequency table. Cohen's Kappa with a 95% CI was used to assess inter-observer agreement between investigators.

Final diagnoses made by health records review were also described using a frequency table. Cohen's Kappa with a 95% CI was calculated to assess inter-observer agreement between ED diagnoses and reviewer's diagnoses.

3.12.2. Analyses for ED Length of Stay

We firstly calculated and compared the median ED length of stay for patients with and without lung POCUS with Mann-Whitney U test to descriptively present crude results. In this crude analysis, patients are separated into two groups: those receiving POCUS at some point during their stay, and those not receiving POCUS. The total time, including the time spent waiting for POCUS, is counted when comparing the times between the groups. If the difference between the groups is attributed to POCUS, it implies the assumption that lung POCUS is performed at the beginning of the time interval (i.e. at registration time) regardless of how long after registration time it actually occurred. In reality, lung POCUS adds new information and can affect the patient's care only after the assessment, not before. While POCUS can either prolong the later care or shorten the total length of time, it is not correct to count the time from registration to POCUS assessment as POCUS cannot affect the duration of time from registration to receiving POCUS. The wait time for POCUS varies for multiple reasons, such as availability of POCUS machines or difficulty of differentiation for diagnoses. Therefore, a comparison of the crude median times between the two groups cannot determine the effect of lung POCUS on the length of time; this analysis is uninformative for that purpose.

To evaluate the effect of lung POCUS on ED length of stay, we used Cox proportional hazards regression analysis. We analyzed time to event where an event was defined as "patient physically leaving the ED." The use of lung POCUS was the primary exposure of interest. To obtain an unbiased assessment of the effect of lung POCUS on ED length of stay, the analysis had to account for the fact that lung POCUS occurs at some time after arriving in the ED. Modeling lung POCUS as a time-fixed variable would have led to a biased estimate of its effect.[64] The time of lung POCUS has to be taken into account in the model as mentioned above, and the probability of event occurrence (patients leaving ED) would change before and after lung POCUS. For this reason, lung POCUS was modelled as a time-dependent predictor. A brief description of this analysis is provided in Appendix C. Note that in this analysis, if lung POCUS was performed right after the registration time and the length of time after the assessment was prolonged due to lung POCUS, the total length of time after POCUS will be attributed to POCUS; on the other hand, if lung POCUS was performed after a long period of time from the registration time and the length of time after the assessment was shortened due to lung POCUS, POCUS will not be unfairly penalized for the length of time waiting for POCUS.

In addition to frequency matching, our analysis also attempted to account for any residual imbalance between the groups using multivariable adjustment. We first examined potential variables for adjustment by comparing selected variables available at the initial assessment in the ED, including patients' vital signs, symptoms, and findings in the physical examination. Only variables known to be strong prognostic factors for outcomes were considered. We used Fisher's exact test for categorical variables, Mann-Whitney U test to compare medians of skewed continuous variables such as time information, and Student t

test to compare means for other continuous variables such as vital signs. Those variables that have some signal of imbalance, using a conservative significance level of $\alpha=0.2$ in the initial statistical testing, were identified as adjustment variables for the final multivariable model. All variables identified were included in the final model - we did not use any elimination procedure from the model.

The effect of lung POCUS on ED length of stay was expressed as an adjusted hazard ratio (HR) together with a 95% CI. Since the event of interest is "leaving the ED," a HR greater than 1 indicates an increased "risk" of patients leaving the ED earlier. For lung POCUS, a HR greater than 1 therefore means lung POCUS shortens ED length of stay. We also estimated the median times of ED length of stay for patients with and without POCUS from the Kaplan-Meier analysis, which accounted for the time-dependent nature of lung POCUS.

We also assessed the proportional hazard assumption using graphical and numerical tests based on the martingale residuals, which is one of the methods used to assess the goodness-of-fit of Cox regression models.[65] For the variables which did not satisfy the proportional hazard assumption, we included interaction terms between the covariates and time in the model; this allowed the effect of the relevant variables to change over time. We used a significance level of $\alpha=0.1$ to assess potential interactions.

3.12.3. Analyses for ED Length of Care

For our second objective, ED length of care was analyzed using Cox proportional hazards regression analysis as described for the primary outcome. The event of interest was "disposition decision."The use of lung POCUS, measured as a time-dependent variable, was the primary exposure of interest. Death in the ED was considered as a censoring event. The

analysis was adjusted for the same baseline risk factors as we described above. The effect of lung POCUS on ED length of care was expressed as an adjusted HR together with a 95% CI. We also estimated the median ED length of care for patients with and without POCUS from the Kaplan-Meier analysis. We assessed the proportional hazard assumption and incorporated relevant interaction terms between the covariates and time in the same method described above.

3.12.4. Analyses for Time to Disease-Specific Treatment

For our third objective, time to disease-specific treatment administration in the ED was first described using Kaplan-Meier curves, which accounted for the time-dependent nature of lung POCUS. Median time to disease-specific treatment, corrected for the time-dependent nature of the exposure, was obtained from the Kaplan-Meier analysis. To assess the statistical significance of lung POCUS, we analyzed time to disease-specific treatment using Cox proportional hazards regression analysis. The event of interest was "disease-specific treatment administration." The use of lung POCUS, measured as a time-dependent variable, was the primary exposure of interest. If patients diagnosed with acute heart failure or COPD did not receive any disease-specific treatment administration in the ED, they were censored at the time of the disposition decision. Patients were also censored if they died in the ED. The analysis was adjusted for the same baseline risk factors as we described above. The effect of lung POCUS on time to disease-specific treatment administration in the ED was expressed as an adjusted HR together with a 95% CI. We used the same strategy of adjustment for potential confounders as above. We assessed whether the proportional hazard assumption was satisfied and if not, we incorporated relevant interaction terms between the covariates and time using the same method described above.

3.12.5. Analyses for Classification Performance of Lung POCUS for Acute Heart Failure

For our fourth objective, the classification performance of lung POCUS to diagnose acute heart failure was determined using sensitivity, specificity, positive predictive value and negative predictive value together with an exact 95% CI. The diagnostic performance of lung POCUS was calculated by comparing the lung POCUS interpretation in the ED and the final diagnosis among patients who received lung POCUS.

We described the classification performance of chest X-ray for identifying acute heart failure by radiologists. Then, we compared the test performance of lung POCUS to that of chest X-ray for identifying heart failure by exact McNemar's test.

3.12.6. Analyses for Incidence of Adverse Events

For our fifth objective, the impact of lung POCUS on the incidence of adverse events was described using unadjusted OR together with a 95% CI from exact logistic regression analysis. Exact logistic regression can provide more robust statistical inference for datasets with a small sample size when; the assumptions of the normal asymptotic methods are not satisfied.[66] We used exact multivariable logistic regression analysis to adjust for possible confounding factors since the event was rare and there was a zero cell, which leads to infinite or undefined estimates in standard logistic regression analysis. We identified potential confounders based on clinically relevant differences between the two groups (with and without lung POCUS). All clinically relevant baseline variables with potential differences between the groups, using statistical significance testing at $\alpha=0.1$, were identified for adjustment. A more stringent criterion for adjustment was used in this analysis

due to the small number of events. We did not use any elimination procedure from the model; all variables identified as potentially important were retained in the model.

3.13. Sample Size Calculation

The sample size for this project was based upon the reality of a restricted timeline for the author. We estimated an ideal sample size as follows. The sample size calculation was determined to ensure adequate power to detect a clinically significant difference in the median ED length of stay between patients with and without POCUS. The assumed median ED length of stay in this patient population was 271 minutes, based on results from a previous Canadian study.[29] We considered a difference of 40 minutes, which is a 15 % reduction, to be clinically relevant based on discussion with an ED research group at The Ottawa Hospital. To detect a difference of 40 minutes with 80% power, using a two-sided α of 0.05 and a conservative ratio of use of lung POCUS to no use of lung POCUS of 1:3, we would require 435 participants with lung POCUS and 1,305 without. If the ratio of use of lung POCUS to no use of lung POCUS was 1:1, we would need 658 participants with lung POCUS and 658 without.

The pragmatic/feasible sample size was estimated as follows. Since the period of collection for this thesis is restricted to 6 months, the maximum achievable sample size for this thesis was anticipated to be about 11 % of that required, according to previous studies showing that our hospital would annually have approximately 100 patients with heart failure and 200 patients with COPD exacerbation as a primary diagnosis, aged of 50 or older, and presented with acute shortness of breath.[21,56]

3.14. Additional Feasibility Considerations

We were allowed to access the required electrical medical records, POCUS image archive, and administrative data to complete the data collection. We did not have any barriers to accessing and using the necessary data sources. Our Emergency Medicine Ultrasonography team in the ED is actively involved in local and multi-centre research projects and accessible to all the ED patients.

3.15. Summary of the Role of Supervisors and Other Individuals Involved in the Research

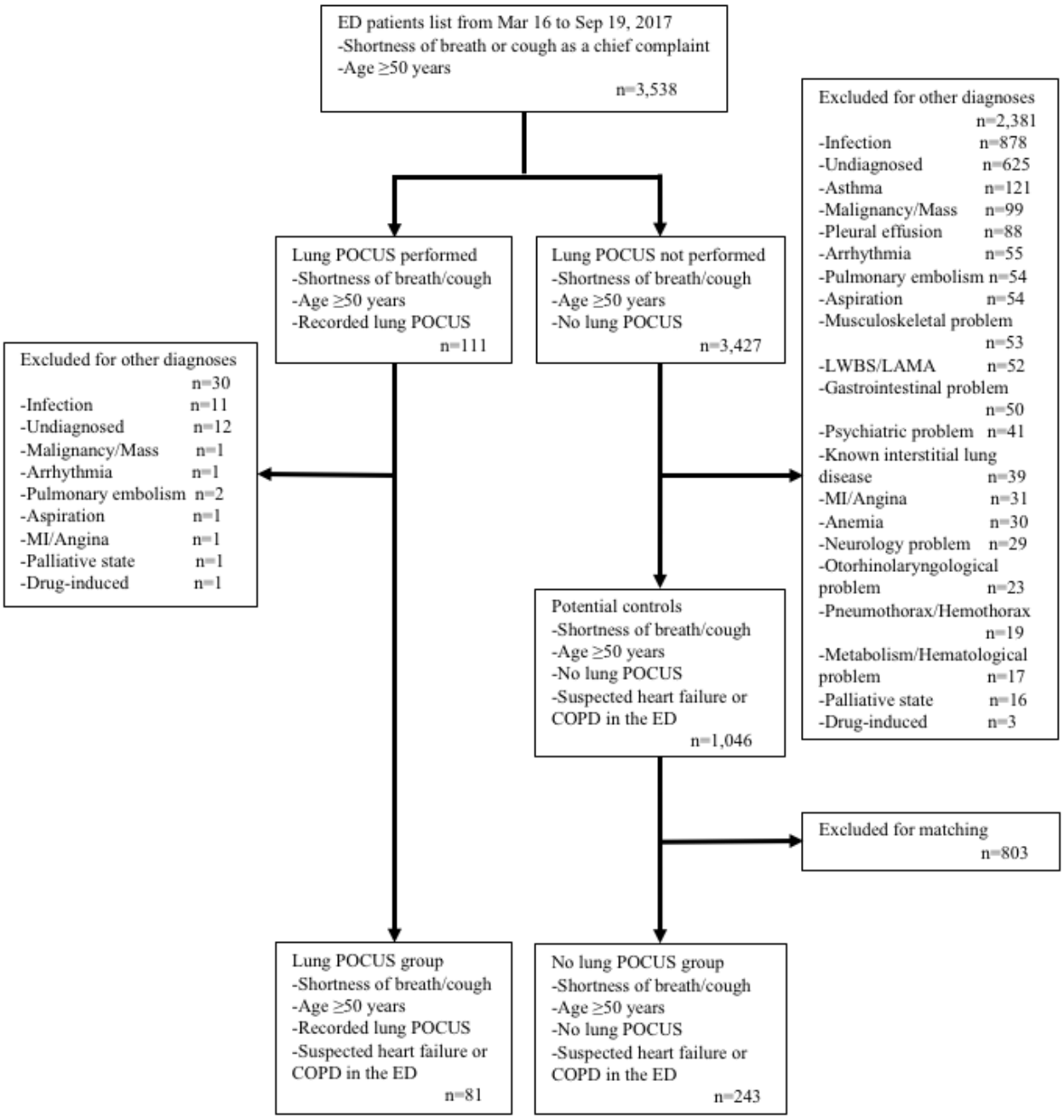
Dr. Christian Vaillancourt supervised this study and provided advice on the conduct of the research project. Dr. Monica Taljaard co-supervised this study and provided advice, especially on the statistical analyses. Dr. Ian G. Stiell is one of the Thesis Advisory Committee members and provided advice on the methodology and clinical implementation of this research. Dr. Michael Y. Woo is another Thesis Advisory Committee member, provided advice especially on POCUS and contributed in reviewing POCUS records for the interpretation and medical charts for the final diagnosis of acute heart failure. All supervisors and committee members critically reviewed the thesis document for its content and scientific accuracy.

Chapter 4. RESULTS

4.1. Identification of Patients for Analysis

Figure 1 summarizes the inclusion and exclusion of patients for analysis. There were 3,538 patients aged 50 or older who visited the ED with shortness of breath or cough as a chief complaint between March 16th, 2017 and September 19th, 2017 at the Ottawa Hospital. Among them, 111 patients (3.1 %) had recorded lung POCUS for the assessment of pulmonary edema in the ED. We excluded 30 patients who had suspected diagnoses of conditions other than acute heart failure or COPD as a cause of shortness of breath or cough. Thus, there remained 81 patients (2.3 %) for inclusion in the study as part of the exposed group. Of the remaining 3,427 patients who did not receive lung POCUS, we excluded 2,381 patients who had a suspected diagnosis of conditions other than acute heart failure or COPD as a cause of shortness of breath or cough. The remaining 1,046 patients (29.6 %) were eligible to be considered for selection into the control group. After the 1:3 matching process, 243 patients among this group were included in our study.

Figure 1. Patient Flow



ED=emergency department; POCUS=point-of-care ultrasonography; COPD=chronic obstructive pulmonary disease; LWBS=left without being seen; LAMA=left against medical advice

4.2. Matching Procedure

We used 1:3 frequency matching by five-year age group, sex, and past medical history of heart failure and COPD. We identified 243 patients from 1,046 patients with age of 50 or older, who visited ED with shortness of breath or cough as a chief complaint with suspicion of exacerbation of heart failure or COPD. The characteristics of the POCUS and matched control patients are summarized in Table 1-a. The median age of the total study cohort was 79 [interquartile range (IQR); 73 to 86] years. Slightly more than half of the patients were female (50.6 %). Most had heart failure (55.6 %) as a past medical history, 33.3 % had COPD, and 19.8 % had both, while 30.9 % had neither known heart failure nor COPD.

Table 1-a. Comparison of Lung POCUS and Control Groups Based on Matching Factors

	Lung POCUS group		**No lung POCUS group**	
Characteristics	**n = 81**		**n = 243**	
Age group, n (%)				
50-54	2	(2.5)	6	(2.5)
55-59	3	(3.7)	9	(3.7)
60-64	3	(3.7)	9	(3.7)
65-69	6	(7.4)	18	(7.4)
70-74	12	(14.8)	36	(14.8)
75-79	18	(22.2)	54	(22.2)
80-84	14	(17.3)	42	(17.3)
85-89	16	(19.8)	48	(19.8)
90-94	6	(7.4)	18	(7.4)
95-99	1	(1.2)	3	(1.2)
>100	0	(0)	0	(0)
Sex, n (%)				
Female	41	(50.6)	123	(50.6)
Male	40	(49.4)	120	(49.4)
Past history of heart failure and/or COPD, n (%)				
Heart failure only	29	(35.8)	87	(35.8)
COPD only	11	(13.6)	33	(13.6)
Heart failure and COPD	16	(19.8)	48	(19.8)
No heart failure or COPD	25	(30.9)	75	(30.9)

POCUS=point-of-care ultrasonography; COPD=chronic obstructive pulmonary disease

4.3. Patient Characteristics

A comparison of lung POCUS and control patients based on characteristics not used in the matching procedure is presented in Table 1-b. In our study sample, we had a higher proportion of patients in the lung POCUS group from the Civic campus (69.1 % vs. 52.7 %). All the patients from the lung POCUS group came to the ED with shortness of breath as a chief complaint whereas nine patients (3.7 %) in the comparison group came with cough as a chief complaint. The median wait time from registration to physician initial assessment time was shorter in the lung POCUS group. The median times were 78 (IQR, 37 to 146) minutes and 98 (IQR, 46 to 156) minutes respectively, and were not statistically different (P=0.17). A higher proportion of patients in the no lung POCUS group had a history of myocardial infarction or angina (37.0 % vs. 49.8 %) or atrial fibrillation (32.1 % vs. 42.8 %), while a higher proportion of patients had an implanted pacemaker (19.8 % vs. 5.4 %) in the lung POCUS group. The proportion of patients taking a calcium channel blocker was higher in the lung POCUS group (39.5 % vs. 29.6 %), and fewer of them took digoxin (2.5 % vs. 7.4 %).

Table 1-c compares signs, symptoms, and findings in the ED between matched groups. Vital signs were very similar in both groups, although the mean body temperature was slightly lower in the lung POCUS group. The Glasgow coma scale medians and IQRs were the same in both groups, though there was a possible sign of imbalance since the range of Glasgow coma scale was 10 to 15 in the lung POCUS group, and 12 to 15 in the comparison group. The proportion of patients with palpitation was lower in the lung POCUS group (1.2 % vs. 5.8 %).

Table 1-b. Comparison of Lung POCUS and Control Groups Based on Factors Not Used in the Matching Process and Analyses to Identify Baseline Imbalances

Characteristics	Lung POCUS group n = 81		No lung POCUS group n = 243		P value*
Location, n (%)					0.01
Civic campus	56	(69.1)	128	(52.7)	
General campus	25	(30.9)	115	(47.3)	
Arrival by ambulance, n (%)	42	(51.9)	130	(53.5)	0.80
Chief complaint, n (%)					0.12
Shortness of breath	81	(100)	234	(96.3)	
Cough	0	(0)	9	(3.7)	
CTAS, n (%)					0.28
1	8	(9.9)	13	(5.3)	
2	41	(50.6)	121	(49.8)	
3	30	(37.0)	104	(42.8)	
4	2	(2.5)	5	(2.1)	
5	0	(0)	0	(0)	
Registration to triage time (minute), median, Q1-Q3	2	1-12	2	0-10	0.58
Registration to physician initial assessment time (minute), median, Q1-Q3	78	37-146	98	46-156	0.17
Other past medical history, n (%)					
Hypertension	61	(75.3)	174	(71.6)	0.57
Diabetes	35	(43.2)	92	(37.9)	0.43
Smoking	31	(38.3)	108	(44.4)	0.37
MI/Angina	30	(37.0)	121	(49.8)	0.054
Atrial fibrillation	26	(32.1)	104	(42.8)	0.12
Chronic kidney disease	21	(25.9)	68	(28.0)	0.78
Pacemaker	16	(19.8)	13	(5.4)	0.0004
Cancer	16	(19.8)	50	(20.6)	1.00
Stroke/TIA	14	(17.3)	32	(13.2)	0.36
Dementia	6	(7.4)	14	(5.8)	0.60
Peripheral vascular disease	5	(6.2)	10	(4.1)	0.54
Asthma	4	(4.9)	17	(7.0)	0.61
Chronic liver disease	1	(1.2)	3	(1.2)	1.00
Home oxygen, n (%)	5	(6.2)	26	(10.7)	0.28
Current cardiac medication, n (%)					
Diuretics	50	(61.7)	148	(60.9)	1.00
Beta blockers	49	(60.5)	134	(55.1)	0.44
Statins	44	(54.3)	144	(59.3)	0.44
ACEIs/ARBs	39	(48.2)	122	(50.2)	0.80
Anti-platelets	34	(42.0)	112	(46.1)	0.61
Ca blockers	32	(39.5)	72	(29.6)	0.10
Nitrates	17	(21.0)	57	(23.5)	0.76
NOAC	15	(18.5)	45	(18.5)	1.00
Warfarin	13	(16.1)	41	(18.5)	1.00
Antiarrhythmics	8	(9.9)	15	(6.2)	0.32
Digoxin	2	(2.5)	18	(7.4)	0.18
Vasodilators	0	(0)	6	(2.5)	0.34
Current respiratory medication, n (%)					
Inhaled beta agonists	33	(40.7)	106	(43.6)	0.70
Inhaled steroids	22	(27.2)	61	(25.1)	0.77
Inhaled anticholinergics	18	(22.2)	62	(25.5)	0.66
Oral steroids	8	(9.9)	28	(11.5)	0.84
PDE4 inhibitors	1	(1.2)	0	(0)	0.25
Methylxanthines	0	(0)	0	(0)	-

*Fisher's exact test for categorical variables or Mann-Whitney U test for continuous variables. P values were underlined if they were less than 0.2.

POCUS=point-of-care ultrasonography; CTAS=Canadian Triage and Acuity Scale; MI=myocardial infarction; TIA=transient ischemic attack, ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor antagonist; NOAC=novel oral anticoagulant drug; PDE4=phosphodiesterase 4

Table 1-c. Comparison of Lung POCUS and Control Groups Based on Symptoms and Findings and Analyses to Identify Baseline Imbalances

	Lung POCUS group		No lung POCUS group		
Characteristics	**n = 81**		**n = 243**		**P value***
Vital signs on arrival, mean (SD)					
Systolic BP (mmHg)	139.7	(29.3)	140.3	(25.1)	0.87
Diastolic BP (mmHg)	77.7	(18.4)	76.2	(16.0)	0.51
Heart rate (/minute)	87.8	(23.5)	89.4	(21.9)	0.58
Body temperature (Celsius)**	36.2	(0.82)	36.4	(0.83)	0.13
Respiration rate (/minute)**	23.7	(7.3)	22.9	(6.0)	0.37
Oxygen saturation (%)	92.0	(6.7)	92.6	(5.5)	0.44
Glasgow coma scale, median, Q1-Q3**	15	15-15	15	15-15	0.06
Symptoms, n (%)					
Cough	48	(59.3)	163	(67.1)	0.23
Sputum production	34	(42.0)	94	(38.7)	0.60
Orthopnea	34	(42.0)	87	(35.8)	0.35
Chest pain	9	(11.1)	25	(10.3)	0.84
Nausea/vomiting	5	(6.2)	12	(4.9)	0.77
Palpitation	1	(1.2)	14	(5.8)	0.13
Physical examination, n (%)					
Peripheral edema	52	(64.2)	141	(58.0)	0.36
Bilateral crackles	51	(63.0)	144	(59.3)	0.60
Bilateral wheezes	23	(28.4)	83	(34.2)	0.41
Chest X-ray, n (%)***	81	(100)	240	(98.8)	0.58
Fluid congestion on X-ray (n=321)	43	(53.1)	117	(48.2)	0.45

*Fisher's exact test for categorical variables, Student t test or Mann-Whitney U test for continuous variables. P values were underlined if they were less than 0.2.
** Data on body temperature were missing for 2 patients, data on respiration rate were missing for 1 patient, and data on Glasgow coma scale were missing for 1 patient
***Chest X-ray interpretation were from final reports by radiologists
POCUS=point-of-care ultrasonography; SD=standard deviation; BP=blood pressure

4.4. Medication Administered in the ED and Final Diagnosis

Medication administered in the ED and final diagnoses are summarized in Table 2. About 90 % of patients were administered disease-specific medication for heart failure or COPD in the ED in both groups. A higher proportion of patients received diuretics in the lung POCUS group (74.1 % vs. 61.3 %), and a lower proportion of patients received steroids

in the lung POCUS group (14.8 % vs. 25.1 %). Antibiotics were given to 14 (17.3 %) patients in the POCUS group, and to 48 (19.8 %) patients in the no POCUS group (P=0.75).

Disease-specific treatment was usually given after physician initial assessment, but was sometimes nurse-initiated and administered before physician initial assessment took place. There were three patients (0.9 %) in the lung POCUS group and eight (2.5 %) in the no lung POCUS group who received disease-specific treatment before physician initial assessment. Among patients in the lung POCUS group, 26 (32.1 %) received disease-specific treatment after physician initial assessment, but before their lung POCUS. There were 7 (8.6 %) patients in the lung POCUS group and 27 (11.1 %) patients in the no POCUS group who did not receive any disease-specific treatment or received disease-specific treatment that was not consistent with their final diagnosis. More than half of patients in both groups were admitted to the hospital, with the division of general internal medicine being the most common subdivision. Using our described reference standard, 64 (79.0 %) patients in the lung POCUS group and 163 (67.1 %) patients in the comparison group were diagnosed with acute heart failure.

Table 2. Medication Administered in the ED and Diagnosis and Comparing

Characteristics	Lung POCUS group n = 81		No lung POCUS group n = 243		P value*
Medicine administered in ED, n (%)	74	(91.4)	218	(89.7)	0.83
Disease-specific treatment for heart failure					
Diuretics	60	(74.1)	149	(61.3)	0.04
Vasodilators	12	(14.8)	41	(16.9)	0.73
Emergency dialysis	1	(1.2)	5	(2.1)	1.00
Disease-specific treatment for COPD					
Beta agonists	19	(23.5)	80	(32.9)	0.13
Anticholinergics	17	(21.0)	70	(28.8)	0.19
Steroids	12	(14.8)	61	(25.1)	0.07
Disease-specific treatment administered before physician initial assessment, n (%)	3	(3.7)	8	(3.3)	1.00
Disease-specific treatment administered after physician initial assessment, before lung POCUS, n (%)	26	(32.1)	-		-
No appropriate treatment in ED, n (%)	7	(8.6)	27	(11.1)	0.68
Initial diagnosis in ED, n (%)					0.14
Acute heart failure	64	(79.0)	168	(69.1)	
COPD	14	(17.3)	68	(28.0)	
Acute heart failure and COPD	3	(3.7)	7	(2.9)	
Disposition, n (%)					0.80
Discharged home	34	(42.0)	108	(44.4)	
Admitted to hospital	47	(58.0)	135	(55.6)	
Admitted to General Medicine	27	(33.3)	73	(30.0)	
Admitted to Cardiology	11	(13.6)	38	(15.6)	
Admitted to Family Medicine	6	(7.4)	13	(5.3)	
Admitted to Respiratology	1	(1.2)	3	(1.2)	
Admitted to Nephrology	1	(1.2)	6	(2.5)	
Admitted to Intensive Care	1	(1.2)	1	(0.4)	
Admitted to Oncology	0	(0)	1	(0.4)	
Final diagnosis, n (%)**					0.17
Acute heart failure	64	(79.0)	163	(67.1)	
COPD	14	(17.3)	66	(27.2)	
Acute heart failure and COPD	3	(3.7)	9	(3.7)	
Other	0	(0)	5	(2.1)	

*Fisher's exact test for categorical variables

**Final diagnosis was the final discharged diagnosis for patients admitted to the hospital, or made with retrospectively reviewing patient's medical charts.

POCUS=point-of-care ultrasonography; ED=emergency department; COPD=chronic obstructive pulmonary disease

4.5. Characteristics of Lung POCUS

The characteristics of lung POCUS are presented in Table 3. The median time to performing lung POCUS was 71 minutes from physician initial assessment. Among those, 18 (22.2 %) patients received lung POCUS within 30 minutes and 36 (44.4 %) within 60 minutes. There were 12 (14.8 %) patients who received lung POCUS after more than 300 minutes from physician initial assessment. The timing of POCUS varied within the timeline of the care in the ED as described in Figure 2.

Although more than half the patients (55.6 %) received lung POCUS before receiving disease-specific treatment, 24.7 % of the patients had their lung POCUS after disease-specific treatment administration and before disposition decision, and 11.1 % received lung POCUS after patients' disposition decision and before they left the ED (e.g. admitted patients who were waiting in the ED for hospital beds might be assessed with lung POCUS for re-assessment).

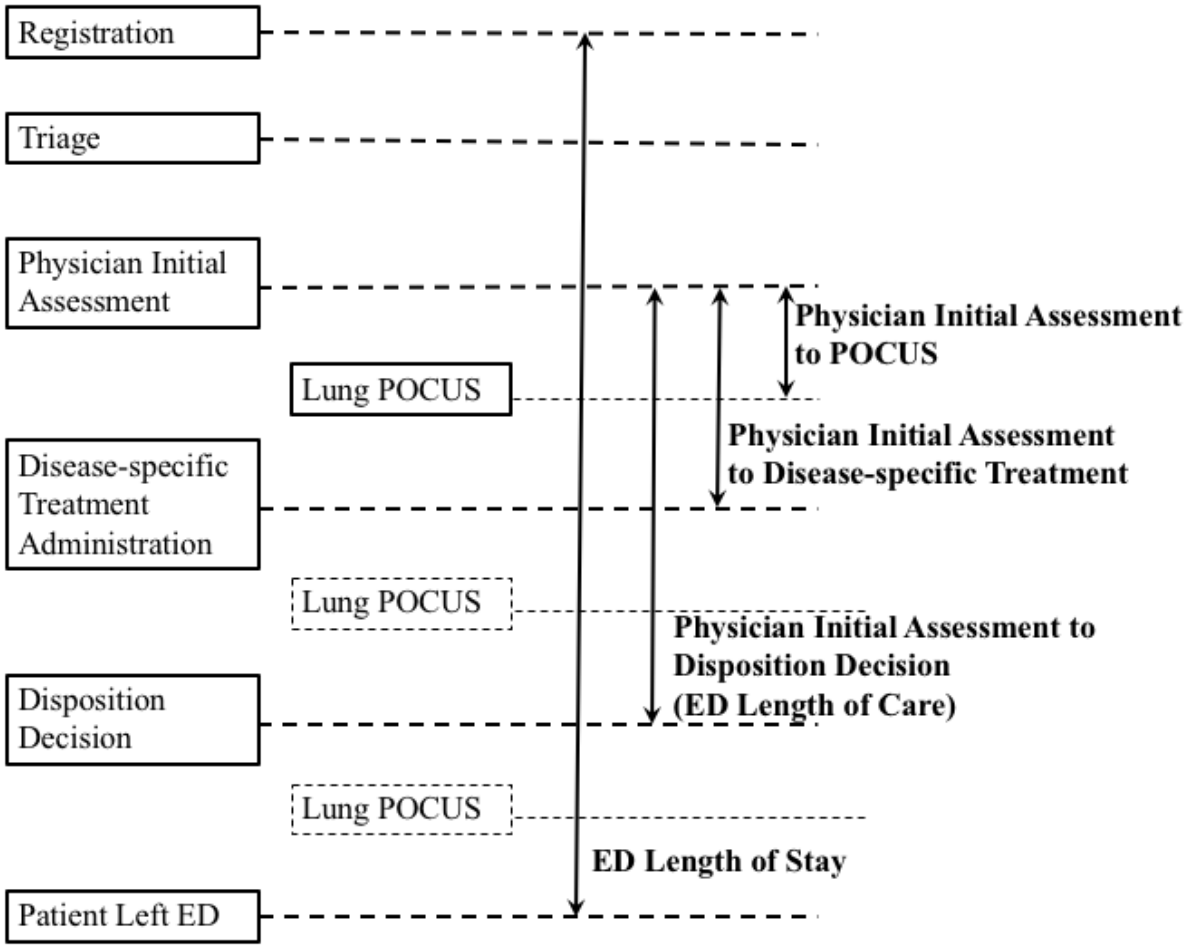
In our study period, one third of ED physicians (24 out of 74) recorded lung POCUS at The Ottawa Hospital. Attending physicians performed 29.6 % of all lung POCUS, 48.1 % were done by residents (postgraduate year 1 to 5), and 22.2 % were done by non-physician sonographers (trained medical students or trained ultrasound technicians). At least 29 patients out of 243 patients in the no POCUS group were seen by ED attending physicians who used lung POCUS during this study period. Thus, POCUS credentialed ED physicians did not always perform lung POCUS. Most of the sonographers assessed and recorded the presence or absence of pleural effusions (71.6 %) and their estimation of the left ventricular function (86.4 %).

Table 3. Characteristics of Lung POCUS

Characteristics	Lung POCUS group n = 81	
Physician initial assessment time to POCUS time (minutes), median, Q1-Q3	71.0	34-153
POCUS time to patient left ED time (minutes), median, Q1-Q3	374.0	221-848
30-minute time range of physician initial assessment time to POCUS time, n (%)		
<30 minutes	18	(22.2)
30 – 59 minutes	18	(22.2)
60 – 89 minutes	12	(14.8)
90 – 119 minutes	6	(7.4)
120 – 149 minutes	5	(6.2)
150 – 179 minutes	4	(4.9)
180 – 209 minutes	4	(4.9)
210 – 239 minutes	2	(2.5)
240 – 269 minutes	0	(0)
270 – 299 minutes	0	(0)
300 minutes or later	12	(14.8)
Timing of POCUS performed, n (%)		
Before disease-specific treatment administration	45	(55.6)
After disease-specific treatment administration, before disposition decision	20	(24.7)
After disposition decision, before patient left ED	9	(11.1)
Sonographers, n (%)		
Attending physicians	39	(29.6)
Residents (PGY 1-5)	25	(48.1)
Non-physician sonographers*	17	(22.2)
POCUS findings, n (%)		
B-lines		
Positive	64	(79.0)
Negative	17	(21.0)
Indeterminate	0	(0)
Pleural effusion		
Positive	35	(43.2)
Negative	23	(28.4)
Indeterminate	0	(0)
Not performed	23	(28.4)
LV function		
Normal/Mild dysfunction	37	(45.7)
Moderate/Severe dysfunction	31	(38.3)
Hyperactive	2	(2.5)
Indeterminate	5	(6.2)
Not performed	6	(7.4)

*Non-physician sonographers refer to trained medical students or trained ultrasound technicians
POCUS=point-of-care ultrasonography; PGY=postgraduate year; LV=left ventricular

Figure 2. Schema of Timeline and Time Intervals in the ED



POCUS may be done anytime after Physician Initial Assessment
ED=emergency department; POCUS=point-of-care ultrasonography

4.6. Inter-Rater Agreements of POCUS Interpretation and Final Diagnosis

There were 81 patients who visited ED with shortness of breath or cough as a chief complaint, aged 50 or older, with recorded lung POCUS in the ED. Among those, 43 (53.1 %) had a completed assessment interpretation form in the Qpath database, and 17 (21.0 %) had their assessment documented in the physicians' chart. There were 21 (25.9 %) lung POCUS with no interpretation which were later interpreted by investigators. There was initial disagreement with two of the 21 reviewed interpretations by study investigators; both

were resolved by way of consensus after discussion between investigators. There was substantial inter-rater agreement as demonstrated by Cohen's kappa of 0.80 (95% CI, 0.53 to 1.00) for the reviewed interpretations by study investigators (Table 4-a).

The final diagnoses were from discharge diagnoses for 182 (56.2 %) patients who were admitted, and from documented diagnoses at the later assessment by other physicians for 91 (28.1 %) patients who were discharged home and seen by another physician later. The remaining 51 (15.7 %) patients were discharged home from the ED with no recorded later assessment, and were reviewed for final diagnoses by one of the study investigators. Though there were disagreements with six out of the 51 diagnoses between those made in the ED and those made by the study investigator using health records reviews, a consensus was reached through discussions with another study investigator. There was also a substantial inter-rater agreement as demonstrated by Cohen's kappa of 0.79 (95% CI, 0.64 to 0.93) for the initial diagnoses by ED physicians and the study investigator's diagnoses (Table 4-b).

Table 4-a. Inter-Rater Agreement of Lung POCUS Interpretation for B-Lines among 21 Patients with No Interpretations by Sonographers

Interpretation by study investigator 1 (MW)	Interpretation by study investigator 2 (SN)		
	Positive	Negative	Indeterminate
Positive	7	1	0
Negative	1	12	0
Indeterminate	0	0	0

Cohen's kappa= 0.80 (95% CI, 0.53 to 1.00)
POCUS=point-of-care ultrasonography; CI=confidence interval

Table 4-b. Inter-Rater Agreement of Final Diagnosis with Study Investigator among 51 Patients Who Discharged Home with No Follow-up Visit

	Diagnosis by study investigator (MW)			
Diagnosis in ED	Acute heart failure	COPD	Acute heart failure and COPD	Other
Acute heart failure	19	0	1	3
COPD	0	26	1	1
Acute heart failure and COPD	0	0	0	0
Other	0	0	0	0

Cohen's kappa= 0.79 (95% CI, 0.64 to 0.93)
COPD=chronic obstructive pulmonary disease; CI=confidence interval

4.7. Factors Identified for Adjustment

We identified 11 factors for statistical adjustment in the multivariable Cox regression analysis, based on clinical importance and statistical significance testing of baseline differences. The selected variables were: location of ED, chief complaint, wait time from registration to physician initial assessment time, Glasgow coma scale, body temperature, past history of myocardial infarction or angina, atrial fibrillation, pacemaker, taking Calcium blockers, taking digoxin and symptom of palpitation. Among those, four factors were deemed to be of sufficient importance to be included in the exact multivariable logistic regression: location of ED, Glasgow coma scale, past history of myocardial infarction or angina, and pacemaker.

4.8. Proportional Hazard Assumption

To analyze the effect of POCUS on time to event outcomes, a multivariable Cox proportional hazards regression was conducted. Before the multivariable regression analysis, we tested the proportional hazard assumption of each covariate using the graphical displays of empirical score process based on martingale residuals for each Cox regression model. Table 5 lists the P values of the test for checking the proportional hazard assumption for each variable. For the analyses of ED length of stay, we found that age group and ED campus location violated the proportional hazard assumption. For the analyses of ED length of care, age group, wait time from registration to physician initial assessment time, and Glasgow coma scale did not meet the proportional hazard assumption. For the analyses of time to disease-specific treatment, Glasgow coma scale, past history of atrial fibrillation, and symptom of palpitation violated the proportional hazard assumption. We created and added interaction terms between these variables and time in each Cox regression into the models. Some examples of the actual graphical displays are presented in Appendix D.

Table 5. Testing the Proportional Hazard Assumption of Each Covariate for Cox Regression Analyses Based on Martingale Residuals

Variables	Registration time to Patient left ED time	Physician initial assessment time to Disposition decision time	Physician initial assessment time to Disease-specific treatment administration time
POCUS	0.92	0.05	0.56
Age	0.02	0.01	0.53
Sex (male)	0.90	0.99	0.58
Past history of heart failure or COPD	0.21	0.51	0.55
Location of ED (Civic campus)	0.04	0.40	0.43
Chief complaint	0.77	0.57	0.28
Wait time (minute)	0.48	<0.0001	0.01
Glasgow coma scale	0.83	0.02	0.14
Body temperature	0.20	0.76	0.39
Past history of MI/Angina	0.98	0.70	0.60
Past history of atrial fibrillation	0.10	0.26	0.03
Past history of pacemaker	0.21	0.44	0.14
Taking Ca blockers	0.42	0.34	0.92
Taking digoxin	0.89	0.69	0.54
Symptom of palpitation	0.81	0.92	0.05

P values are underlined if the level of significance is less than 0.1
POCUS=point-of-care ultrasonography; COPD=chronic obstructive pulmonary disease; ED=emergency department; MI=myocardial infarction

4.9. Crude and Time-Dependent Length of Time

The crude descriptive analyses of time to event outcomes are presented in Table 6. The median ED length of stay was 620 (IQR, 420 to 1,148) minutes for the lung POCUS group and 615 (IQR, 393 to 1,186) minutes for the comparison group. The median ED length of care was 351 (IQR, 281 to 488) minutes for the lung POCUS group and 341 (IQR, 214 to 527) minutes for the comparison group. These crude differences in the median times between the groups are presented for descriptive information only, and are not a valid comparison of the effect of lung POCUS. That is because the analysis does not account for the time-dependent nature of lung POCUS; in effect, the crude analysis attributes the entire

time of waiting (including the time of waiting for lung POCUS) to the POCUS group. Moreover, the crude analysis does not allow for the fact that some patients received lung POCUS only after their treatment.

To show the effect of properly accounting for the time-dependent nature of lung POCUS, we conducted the time-dependent Kaplan-Meier analysis. The median times of ED length of stay and ED length of care were slightly shorter in the lung POCUS group than those of no lung POCUS group, though they were not statistically significant. However, this analysis showed that the median time to disease-specific treatment administration was shorter in the lung POCUS group than in the comparison group (61 minutes vs. 92 minutes; Figure 3).

The crude median times showed the opposite results, potentially because patients who needed the lung POCUS assessment as an additional test to diagnose might have stayed longer in the ED before lung POCUS, although we tried to create a comparable no POCUS group by frequency matching. This is not surprising, since we have observed that lung POCUS was frequently performed more than 60 minutes after physician initial assessment.

Table 6. Description and Comparison of Crude and Time-Dependent Length of Time between Lung POCUS Group and Controls

Length of Time (minutes), median, Q1-Q3	Lung POCUS group n = 81		No lung POCUS group n = 243		P value*
Crude length of time					
Registration time to patient left ED time	620.0	420 to 1148	615.0	393 to 1186	0.70
Physician initial assessment time to disposition decision time	351.0	281 to 488	341.0	214 to 527	0.43
Physician initial assessment time to disease-specific treatment administration time (n=279)**	81.0	47 to 130	71.5	38 to 146	0.57
Accounting for the time-dependent nature of POCUS***					
Registration time to patient left ED time	592.0	373 to 1004	626.0	405 to 1212	0.36
Physician initial assessment time to disposition decision time	323.0	239 to 478	343.0	277 to 528	0.31
Physician initial assessment time to disease-specific treatment administration time	61.0	22 to 99	92.0	49 to 203	0.0005

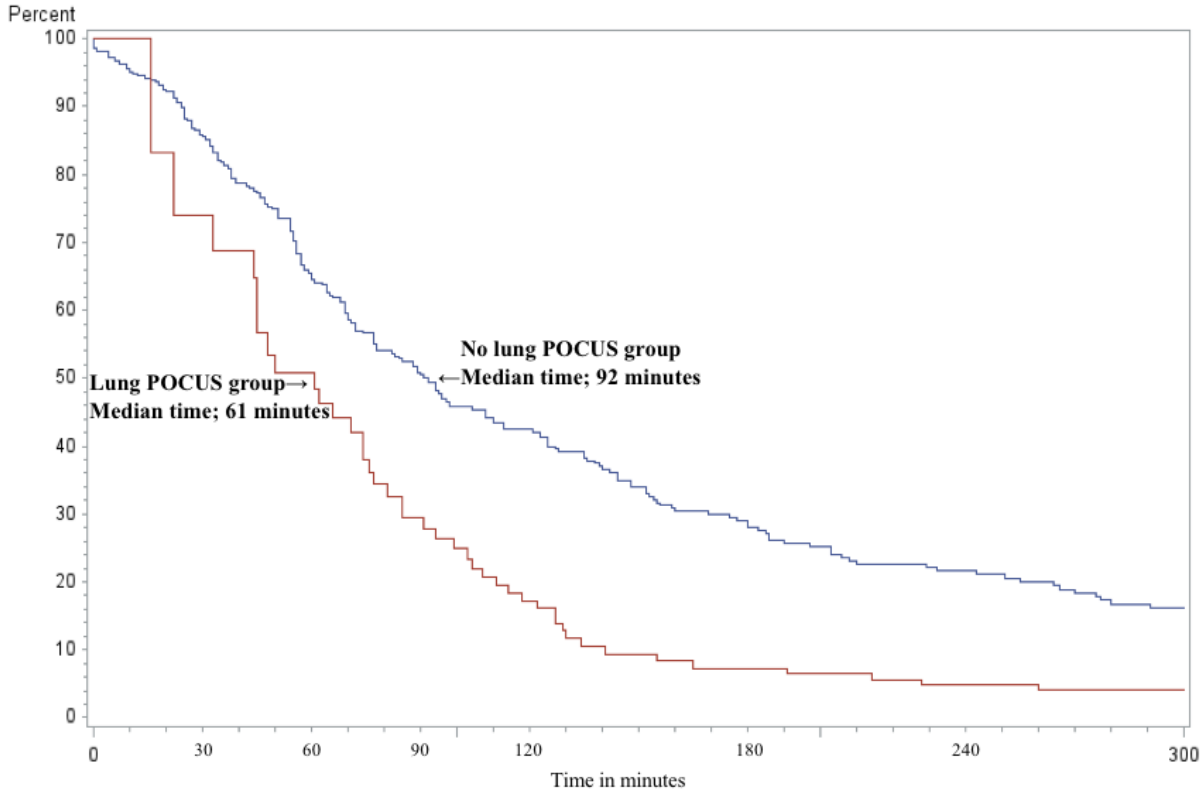
*Mann-Whitney U test for continuous variables or Cox regression analysis to account for the time-dependent nature of POCUS

**n=34 patients did not receive appropriate disease-specific treatment in the ED and n=11 patients received disease-specific treatment before physician initial assessment, and were excluded from this analysis

***The median times are from Kaplan-Meier analysis, which accounted for the time-varying nature of POCUS

POCUS=point-of-care ultrasonography; ED=emergency department

Figure 3. Kaplan-Meier Curves for Time to Disease-Specific Treatment for Patients with and without Lung POCUS, Accounting for POCUS as a Time-Dependent Variable



POCUS=point-of-care ultrasonography

4.10. Cox Regression Analyses with Time-Dependent Variable

To test the statistical significance of differences in times to events between the groups accounting for the time-dependent nature of lung POCUS, Cox regression analyses were conducted with lung POCUS modelled as a time-dependent variable. Unadjusted and adjusted HRs from the Cox regression analyses are summarized in Table 7. HRs were adjusted for baseline imbalance and interaction terms. Adjusted HRs for other variables are provided in Appendix E. A HR of greater than one corresponds to a shortened time resulting from the benefit of using lung POCUS, whereas a HR of less than one corresponds to an increased length of time. Lung POCUS did not significantly impact ED length of stay

(adjusted HR, 1.11 [95% CI, 0.85 to 1.46], P=0.44) or ED length of care (adjusted HR, 1.05 [95% CI, 0.79 to 1.40], P=0.73). That said, patients evaluated with lung POCUS received disease-specific treatment faster (adjusted HR, 1.50 [95% CI, 1.05 to 2.15], P=0.03). According to the Kaplan-Meier analysis, the median saved time to disease-specific treatment administration attributed to lung POCUS was 31 minutes.

Table 7. Unadjusted and Adjusted Hazard Ratios Comparing Time to Discharge, Disposition, and Disease-Specific Treatment for POCUS Group Versus No POCUS Group by Time-Dependent Cox Regression Analyses

	Unadjusted			Adjusted**		
Length of Time	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Registration time to patient left ED time	1.13	0.87 to 1.45	0.36	1.11	0.85 to 1.46	0.44
Physician initial assessment time to disposition decision time	1.15	0.88 to 1.49	0.31	1.05	0.79 to 1.40	0.73
Physician initial assessment time to disease-specific treatment administration time*	1.79	1.29 to 2.48	0.0005	1.50	1.05 to 2.15	0.03

*n=11 patients received disease-specific treatment before physician initial assessment and were excluded from the analysis. n=279 had event (received the appropriate disease-specific treatment in the ED) and n=34 were censored
**Analysis was adjusted for location of ED, chief complaint, wait time, Glasgow coma scale, body temperature, past history of MI/Angia, atrial fibrillation, pacemaker, taking Ca blocker, taking digoxin and symptom of palpitation as well as matching factors (age group, sex, and past history of heart failure/COPD. Interaction terms based on martingale residuals were involved in each analysis
POCUS=point-of-care ultrasonography; ED=emergency department; SE=standard error; HR=hazard ratio; CI=confidence interval; MI=myocardial infarction; COPD=chronic obstructive pulmonary disease

4.11. Effect of Timing of POCUS on Time to Disease-Specific Treatment

We also assessed the effect of the timing of lung POCUS within the time-dependent Cox regression analysis. In particular, we created time-dependent indicators for lung POCUS within 30 minutes from physician initial assessment, 30 to 60 minutes, 60 minutes to 120 minutes, and later. Table 8 shows the unadjusted and adjusted HRs in each timing

strata of lung POCUS. HRs were adjusted for baseline imbalance and interaction terms. Adjusted HRs were greater than one if lung POCUS was done within 30 minutes, which means lung POCUS can speed up the disease-specific treatment administration when it is done within 30 minutes. Adjusted HRs were significantly less than one if lung POCUS was done after 120 minutes from physician initial assessment. However, this is difficult to interpret because four patients out of nine patients who received lung POCUS after 120 minutes did not receive disease-specific treatment in the ED (i.e. these patients were censored at the time of disposition decision time in the analyses). The censoring rate of the patients who received lung POCUS after 120 minutes was 44 %, whereas that of the reference group was 9.9 %. This could potentially bias the results against lung POCUS.

Table 8. Unadjusted and Adjusted Hazard Ratios Comparing Time to Disease-Specific Treatment by POCUS Performed Time among 52 Patients with Lung POCUS Performed before the Treatment Administration to No POCUS Group

POCUS performed time	N of patients	Unadjusted*			Adjusted**		
		HR	95% CI	P value	HR	95% CI	P value*
< 30 minutes	14	2.00	1.16 to 3.45	0.01	1.53	0.84 to 2.78	0.17
30 – 60 minutes	17	0.97	0.58 to 1.61	0.90	0.80	0.46 to 1.39	0.43
60 – 120 minutes	12	0.66	0.35 to 1.24	0.20	0.55	0.29 to 1.07	0.08
120 minutes or later	9	0.21	0.09 to 0.52	0.0007	0.12	0.04 to 0.31	<0.0001

*Total of 313 observations were used for analysis. n=279 had event (received the appropriate disease-specific treatment in the ED) and n=34 were censored. Time of POCUS was considered as a time-dependent variable in the Cox regression model

**Analysis was adjusted for location of ED, chief complaint, wait time, Glasgow coma scale, body temperature, past history of MI/Angina, atrial fibrillation, pacemaker, taking Ca blocker, taking digoxin and symptom of palpitation as well as matching factors (age group, sex, and past history of heart failure/COPD. Interaction terms (wait time by time, past history of atrial fibrillation by time, and symptom of palpitation by time) based on martingale residuals were involved.

POCUS=point-of-care ultrasonography; SE=standard error; HR=hazard ratio; CI=confidence interval; ED=emergency department; MI=myocardial infarction; COPD=chronic obstructive pulmonary disease

4.12. Classification Performance of Lung POCUS and Chest X-Ray

Table 9-a describes the classification performance of lung POCUS for identifying acute heart failure compared to the final diagnoses by the reference standard, which were the discharge diagnoses for patients admitted to the hospital, ED diagnoses with confirmation by another physician, or diagnoses made by medical chart reviews. ED physicians correctly identified acute heart failure by lung POCUS with a sensitivity of 92.5 % (95% CI, 83.4 to 97.5 %), specificity of 85.7 % (95% CI, 57.2 to 98.2 %), positive predictive value of 96.9 % (95% CI, 89.2 to 99.6 %), and negative predictive value of 70.6 % (95% CI, 44.0 to 89.7 %).

Table 9-b describes the classification performance of chest X-ray for identifying acute heart failure by radiologists. Radiologists correctly identified acute heart failure by chest X-ray in the official reports with a sensitivity of 64.0 % (95% CI, 57.5 to 70.1 %), specificity of 89.4 % (95% CI, 80.9 to 95.0 %), positive predictive value of 94.4 % (95% CI, 89.6 to 97.4 %), and negative predictive value of 47.2 % (95% CI, 39.3 to 55.2 %).

Table 9-a. Classification Performance of Lung POCUS for Identifying Acute Heart Failure in 81 Patients Who Underwent Lung POCUS

	Final diagnosis of acute heart failure*	
Lung POCUS(n=81)**	Yes	No
Positive	62	2
Negative	5	12

Sensitivity; 0.925 (95% CI, 0.834 to 0.975)
Specificity; 0.857 (95% CI, 0.572 to 0.982)
Positive predictive value; 0.969 (95% CI, 0.892 to 0.996)
Negative predictive value; 0.706 (95% CI, 0.440 to 0.897)

*Final diagnosis was the discharge diagnosis for patients admitted to the hospital, ED diagnosis with confirmation by another physician, or diagnosis made by medical chart reviews
**POCUS is positive if more than two positive B-lines per side are observed when the examination is performed on eight chest areas (two anterior and two lateral for each side)
POCUS=point-of-care ultrasonography; CI=confidence interval

Table 9-b. Classification Performance of Chest X-Ray for Identifying Acute Heart Failure in 321 Study Patients Who Underwent Chest X-Ray

	Final diagnosis of acute heart failure*	
Congestion in X-ray(n=321)**	Yes	No
Positive	151	9
Negative	85	76

Sensitivity; 0.640 (95% CI, 0.575 to 0.701)
Specificity; 0.894 (95% CI, 0.809 to 0.950)
Positive predictive value; 0.944 (95% CI, 0.896 to 0.974)
Negative predictive value; 0.472 (95% CI, 0.393 to 0.552)

*Final diagnosis was the final discharged diagnosis for patients admitted to the hospital, ED diagnosis with confirmation by another physician, or diagnosis made by medical records reviews
**Interpretation of chest X-ray was done by radiologists.
CI=confidence interval

4.13. Comparing Performance of Chest X-Ray and POCUS

We compared the test performance of lung POCUS to that of chest X-ray for identifying acute heart failure. Table 9-c shows that the sensitivity of lung POCUS was significantly better than that of chest X-ray (P=0.0003) by exact McNemar's test analyzed

among 66 patients who were diagnosed with acute heart failure with the reference standard. Table 9-d shows that the specificity of lung POCUS was not significantly better than that of Chest X-ray (P=1.00) by exact McNemar's test analyzed among 14 patients who were not diagnosed acute heart failure.

Table 9-c. Comparing Performance of Chest X-Ray and POCUS for Identifying Acute Heart Failure among 66 Patients with Acute Heart Failure Who Received Both Tests

	Chest X-ray	
Lung POCUS (n=66)	Positive	Negative
Positive	38	23
Negative	4	1

The sensitivity of lung POCUS was significantly better than that of chest X-ray (P=0.0003) by exact McNemar's test

Final diagnosis was the final discharged diagnosis for patients admitted to the hospital, ED diagnosis with confirmation by another physician, or diagnosis made by health records reviews
POCUS=point-of-care ultrasonography; ED=emergency department; CI=confidence interval

Table 9-d. Comparing Performance of Chest X-Ray and POCUS for Identifying Acute Heart Failure among 14 Patients without Acute Heart Failure Who Received Both Tests

	Chest X-ray	
Lung POCUS (n=14)	Positive	Negative
Positive	0	2
Negative	1	11

The specificity of lung POCUS was not significantly better than that of chest X-ray (P=1.00) by exact McNemar's test

Final diagnosis was the final discharged diagnosis for patients admitted to the hospital, ED diagnosis with confirmation by another physician, or diagnosis made by health records reviews
POCUS=point-of-care ultrasonography; ED=emergency department; CI=confidence interval

4.14. Incidence of Adverse Events

We explored incidence of adverse events in both groups. Table 10-a shows incidence of adverse events, and Table 10-b summarizes unadjusted and adjusted ORs from exact logistic regression analyses. After the multivariable adjustment, we found no difference in administration of potentially unnecessary treatment or unscheduled ED visits within 7 days. Inhaled beta agonists and inhaled anticholinergics were the majority of potentially unnecessary treatment. These patients were likely to have been initially suspected of having COPD and diagnosed with acute heart failure later. All of the potentially unnecessary treatment were administered after physician initial assessment. We did not observe any serious adverse events such as death in the ED due to the potentially unnecessary treatment.

However, we found a trend toward a decreased incidence of inappropriate ED diagnosis in the lung POCUS group. There was no inappropriate ED diagnosis in the lung POCUS group in our study. We did not observe any actual harm to the patients who received unnecessary treatment such as death in the ED.

Table 10-a. Incidence of Adverse Events for POCUS Group Versus No POCUS Group

	Lung POCUS group	No lung POCUS group
Adverse events	**n = 81**	**n = 243**
Potentially unnecessary treatment*, n (%)	8 (9.9)	30 (12.4)
Beta agonists	5 (6.2)	23 (9.5)
Anticholinergics	3 (3.7)	18 (7.4)
Steroids	1 (1.2)	6 (2.5)
Diuretics	2 (2.5)	4 (1.6)
Vasodilators	1 (1.2)	2 (0.8)
Return within 7 days, n (%)	3 (3.7)	12 (4.9)
Inappropriate ED diagnosis, n (%)	0 (0)	10 (4.1)

*Potentially unnecessary treatment is defined as administration of disease-specific treatment for inappropriate diagnosis based on the final diagnosis
POCUS=point-of-care ultrasonography

Table 10-b. Unadjusted and Adjusted Odds Ratios Comparing Incidence of Adverse Events for POCUS Group Versus No POCUS Group. Analysis was Adjusted for Location of ED, Glasgow Coma Scale, and Past History of MI or Angina, Pacemaker.

	Unadjusted			Adjusted		
Adverse events	**OR**	**95% CI**	**P value***	**OR**	**95% CI**	**P value***
Potentially unnecessary treatment**	0.78	0.30 to 1.84	0.71	0.62	0.22 to 1.54	0.37
Return within 7 days	0.74	0.13 to 2.85	0.92	0.80	0.14 to 3.15	1.00
Inappropriate ED diagnosis	0.21	0 to 1.03	0.054	0.25	0 to 1.24	0.08

*Exact test in logistic regression analysis
**Potentially unnecessary treatment is defined as administration of disease-specific treatment for inappropriate diagnosis based on the final diagnosis
POCUS=point-of-care ultrasonography; ED=emergency department; MI=myocardial infarction; OR=odds ratio; CI=confidence interval

Chapter 5. DISCUSSION

5.1. Summary of Main Findings

In this thesis, we sought to determine the clinical impact of lung POCUS on patient-oriented outcomes. We did not observe statistical differences of ED length of stay or ED length of care by using lung POCUS among patients with suspected acute heart failure or COPD. However, the adjusted HR analyses confirmed that lung POCUS resulted in faster administration of disease-specific treatments for acute heart failure and COPD patients. The reduction in median times to appropriate treatment administration resulting from lung POCUS was 31 minutes according to the Kaplan-Meier analysis.

Lung POCUS was highly sensitive and specific in identifying acute heart failure, and had higher sensitivity than chest X-ray. We did not find differences of pre-defined adverse events by lung POCUS. However, we found a trend of lower incidence of adverse events in the lung POCUS group, including potentially unnecessary treatment administration, unscheduled ED visits ≤7 days, and inappropriate ED diagnosis. These results may potentially be clinically relevant since the point estimates of the ORs were low, especially for incidences of potentially unnecessary treatment and inappropriate ED diagnosis.

This thesis work suggests that lung POCUS can accurately be performed by ED physicians, and could significantly decrease the time to administration of appropriate treatment for patients visiting the ED with suspected acute heart failure or COPD.

5.2. Interpretation

5.2.1. ED Length of Stay

We chose ED length of stay as a primary outcome to look at the time reduction by lung POCUS for those with suspected acute heart failure or COPD in the ED. After

successfully matching and adjusting with baseline imbalances of patient characteristics between groups, we found no difference in ED length of stay between them, even though we accounted for the time-dependent nature of POCUS. Although the point estimates of HRs were slightly larger than one and the results from the Kaplan-Meier analysis were consistent, they were not statistically significant.

5.2.2. ED Length of Care

We assessed ED length of care as a secondary outcome to observe more direct impact on time in the ED. We hypothesised we could observe a time reduction in ED length of care by lung POCUS because it could directly affect the physicians' decision making. After successfully matching patient characteristics between groups, we found no difference in ED length of care between them even though we accounted for the time-dependent nature of POCUS. Although the point estimates of HRs were slightly larger than one and the results from the Kaplan-Meier analysis were consistent, they were not statistically significant.

5.2.3. Time to Disease-Specific Treatment Administration

We have chosen time to disease-specific treatment administration as one of our secondary patient-relevant outcomes. We hypothesised we could observe a time reduction by lung POCUS because it could directly affect the timing of accurate diagnosis and accurate treatment. Our study successfully demonstrated the time-saving effect of lung POCUS for the assessment of acute heart failure in the time to disease-specific treatment in the ED.

The discrepancy between the crude median times and the median times from the Kaplan-Meier analysis was due to time-dependent bias.[64] The time-dependent nature of POCUS had to be considered in the analyses because some of the lung POCUS were

performed in a late phase of patient care, possibly due to shift change of ED physicians, or perhaps the availability of the POCUS machine. As a result, the crude median time to disease-specific treatment administration appeared to be longer in the POCUS group, but after adjusting for the time to POCUS using the Kaplan-Meier analysis, it was shorter in the POCUS group. The point estimate of the adjusted HR was larger than one, which suggests that lung POCUS shortened the time to disease-specific treatment administration, consistent with the results from the Kaplan-Meier analysis.

We also demonstrated the effect of delays in time to receiving POCUS on disease-specific treatment administration. For this analysis, we again used Cox regression analyses with a time-dependent variable but here, we treated POCUS not as a binary variable but as a categorical variable defined by different timings of lung POCUS. The adjusted HR was greater than one when lung POCUS was performed within 30 minutes, which suggests that lung POCUS shortened the time to treatment administration as long as it was performed within 30 minutes. On the other hand, the adjusted HR was significantly less than one when lung POCUS was performed later than 120 minutes following physician initial assessment. This HR is difficult to interpret not only because of the substantial difference of censoring rates, but also the small number of observations in the stratified group. Moreover, patients who received lung POCUS after 120 minutes might have been in a milder condition than other patients in the lung POCUS group, since they stayed in the ED without receiving disease-specific treatment until receiving lung POCUS. This might serve to delay the time from to physician's order of medication to administration time compared to severe patients who need to be cared for by multiple professionals in the ED.

5.2.4. Classification Performance of Lung POCUS for Acute Heart Failure

One of the secondary aims of our study was to evaluate the classification performance of lung POCUS for acute heart failure with our reference standard. The sensitivity, specificity, positive predictive value, and negative predictive value of lung POCUS to identify acute heart failure in the ED were very high. The test performance of lung POCUS by ED physicians was significantly better in sensitivity, and similar in specificity compared to those of chest X-ray interpreted by radiologists. The inter-rater agreement of interpretation of lung POCUS interpretation by two reviewers for scans without interpretation by sonographers was substantial. The inter-rater agreement of the final diagnosis for those without known later visit after being discharged home between ED diagnosis and reviewer was also substantial.

5.2.5. Incidence of Adverse Events

Lastly, we explored the clinical impact on the incidence of adverse events due to the accuracy of lung POCUS for acute heart failure. We did not observe statistically significant differences in the administration of potentially unnecessary treatment or unscheduled return visits to the ED within 7 days by the use of lung POCUS. There was a tendency of having less inappropriate ED diagnosis in the lung POCUS group. Although all the point estimates we measured were in favor of lung POCUS group, our sample size was too small to detect a difference given the low incidence rate of adverse events.

5.3. Comparison to Previous Studies

To our knowledge, no other study has been published examining the difference of ED length of stay by lung POCUS specifically, although there are several studies in other modalities of POCUS that could decrease ED length of stay. Blaivas and colleagues

conducted a retrospective analysis that showed the POCUS of the gallbladder by ED physicians decreased ED length of stay by 7 % (22 minutes) compared to radiology-performed US.[47] Elikashvili and colleagues performed a prospective observational study describing that POCUS for children with suspected appendicitis decreased radiation exposure and ED length of stay from 288 minutes to 154 minutes.[46] Chiem and colleagues demonstrated that pelvic POCUS by EP physicians for female patients who require pelvic US reduced ED length of stay by 108 minutes compared to radiology-performed US in their prospective observational study.[49]

A Danish randomized controlled study examining the impact of POCUS assessment, including lung POCUS, in patients admitted with respiratory symptoms showed more patients had a correct diagnosis within 4 hours after admission to the ED.[67] This study implies the time-effectiveness of lung POCUS at making a timely diagnosis for dyspneic patients.

There is a previous prospective observational study comparing the time to diagnosis by using lung POCUS for patients with shortness of breath in the ED. Zanobetti and colleagues reported that lung POCUS in dyspneic patients could reduce the time to diagnosis. They showed that the average time to diagnosis in the ED was 186 minutes with a regular evaluation, and that the average time to formulate the ultrasound diagnosis when evaluated by another independent sonographer was 24 minutes, which was significantly faster (P=0.025) with a higher sensitivity for acute heart failure but a lower sensitivity for COPD compared to ED diagnoses.[68] The study design was different since lung POCUS in their study was performed by independent sonographers whereas our study was in a real clinical setting.

Martindale and colleagues published a systematic review of lung POCUS in the ED for patients with undifferentiated dyspnea in 2015 and included 8 studies for test performance of lung POCUS for acute heart failure. They showed that the sensitivity was 85.3% (95% CI, 82.8 to 87.5%) and the specificity was 92.7% (95% CI, 90.9 to 94.3%). They also illustrated that chest radiographic findings of pulmonary edema had a sensitivity of 56.9% (95% CI, 54.7 to 59.1%) and a specificity of 89.2% (95% CI, 87.9 to 90.4%).[38] Our results are very consistent with theirs.

There is a paucity of evidence showing the difference of adverse events rate. In a study by Singer and colleagues, 21% of patients who were admitted with acute decompensated heart failure without a history of COPD received bronchodilators in the ED or by paramedics.[53] This incidence is higher than our results (12.4 % in no POCUS group) because the study population was different. We included patients who were discharged home from the ED, and considered heart failure-specific treatment for patients without acute heart failure also as inappropriate treatment. We did not include the treatment provided by paramedics. However, we were able to provide the prevalence of potentially unnecessary treatment for patients who were suspected of having acute heart failure or COPD in the ED.

5.4. Strengths

We successfully created a dataset with 1:3 frequency matching to reduce the risks of confounding and increase the statistical power of our analyses. The information of lung POCUS was reliable since it was documented prospectively in the Qpath digital archiving system. We analyzed the difference in ED length of stay, ED length of care, and time to disease-specific treatment administration between the groups with Cox regression analysis with a time-dependent variable to avoid time-dependent bias due to the timing of lung

POCUS.[64] We checked the proportional hazard assumption using martingale residuals and included interaction terms for the appropriate Cox regression analysis with a time-dependent variable.

We correctly demonstrated the time reduction by lung POCUS using Cox regression analysis with a time-dependent variable to avoid time-dependent bias. We also conducted the Kaplan-Meier analysis accounting for the time-dependent nature of lung POCUS to calculate the median times and the saved time by lung POCUS for the time to disease-specific treatment administration. Furthermore, we successfully illustrated the Kaplan-Meier curves to visualize our results of time to disease-specific treatment administration. The results of both analyses were consistent and we were able to determine the estimated disease-specific treatment administration time saved by lung POCUS.

We created a reliable dataset with careful documentations of lung POCUS and careful reviews for lung POCUS interpretation. Our reference standard for the final diagnosis was also reliable due to careful reviews with substantial inter-rater agreement to include the patients who were discharged home from the ED. Our study provided classification performance of lung POCUS to identify acute heart failure in a real clinical setting with a great educational program for POCUS. We used an 8-zone technique for the lung POCUS assessment, which is recommended in the international evidence-based recommendations for point-of-care lung ultrasound.

We calculated ORs for the incidence of adverse events to demonstrate the potential clinical impact of lung POCUS accuracy. We believe the administration of potentially unnecessary treatment, unscheduled return visits to ED within 7 days, and inappropriate ED

diagnosis are important in terms of patient safety, medical management by physicians and medical cost.

5.5. Limitations

Due to the pragmatic timeline restrictions of 6 months for the student to complete data collection, we did not have an adequate sample size to detect statistically significant differences of ED length of stay and ED length of care. Our results showed that the proportion of the usage of lung POCUS in our study population in the ED was small, in spite of the Emergency Medicine Ultrasonography team at The Ottawa Hospital providing a strong educational program for POCUS. The relatively low POCUS usage may have been observed for various reasons, including machine availability, time to get the machine, perception of POCUS benefit by ED physicians, and lack of specific lung POCUS training for credentialing. ED physicians may have chosen not to perform lung POCUS if they were confident enough to make clinical decisions without it, since lung POCUS is not currently a broadly accepted standard care for use in dyspneic patients. The actual ED length of stay and ED length of care were longer than the assumed values we used for sample size calculation. Moreover, we observed a smaller difference (34 minute difference in median times) than we postulated; the minimal clinically important difference for ED length of stay was 40 minutes when we calculated the sample size. For the analyses of the incidence of pre-defined adverse events, we needed to have a larger sample size to observe the potential difference because the incidence rates were low.

Another potential reason for the non-significant differences of ED length of stay and ED length of care was because there were multiple other factors affecting wait times, for example, increased hospital bed occupancy is associated with ED length of stay, and the

specialty consultation is associated with ED length of care and ED length of stay.[29,55] These factors cannot be controlled by ED physicians.

By nature of health records review, we could not specify the intended use of lung POCUS or whether it was for diagnosis, confirmatory, monitoring, or other reasons. That said, we did exclude purely educational scans from the Qpath data. The early diagnostic use of lung POCUS may have a different impact on the ED length of stay and ED length of care compared to its later use, which may be less likely to change the ED clinical course of patients. Lung POCUS was sometimes performed more than 60 minutes after initial assessment because additional information might have been needed after knowing patients were not responding well to treatment. Lung POCUS assessments might have been performed after appropriate treatment administration in order to confirm the diagnoses or to assess the patients' response to treatment. ED physicians might not have had immediate access to the POCUS machines. We also did not collect information on the shift changes of ED physicians. Physicians may perform lung POCUS to make sure the current assessment and treatment are appropriate. In this case, lung POCUS cannot affect ED length of stay and ED length of care unless they find inappropriate management or treatment through their scans.

A substantial number of patients who received lung POCUS also received a heart assessment. Since ED physicians would make a clinical decision based on all available information, results of the heart assessment might also influence their decision. Although we could not adjust the outcomes of interest for the presence of the heart assessment, we assumed the impact of the heart assessment would be limited since the reported classification performance of the heart assessment was not as high for lung POCUS.[38]

In our POCUS data, some scans were performed by non-physician sonographers, who were trained medical students or trained ultrasound technicians, although POCUS is usually performed and interpreted by the physician at the bedside. Credentialed non-physician sonographers helped the busy ED physicians in the real clinical setting. Although there might be a time gap between the time lung POCUS was performed and the time ED physicians knew the findings, it would be minimal since the sonographers reported the findings to physicians and documented them immediately. The time loss may bias the results in favor of no POCUS.

ED length of stay and ED length of care can be inherently correlated with the specific clinician looking after a given patient, which we did not adjust for. This may affect our results since the recent literature found significant inter-physician differences in ED length of stay.[69] However, it was difficult to control for this factor in our study to preserve clinical privacy.

Our target population included patients who were suspected of having acute heart failure or COPD in the ED. We used suspected diagnoses in the ED to include the patients, which may have been affected by the finding of lung POCUS in the lung POCUS group. This may introduce classification bias, but we showed that our baseline characteristics between the groups were comparable. This was possibly because COPD was the most prevalent alternative diagnosis in our population. We also adjusted for baseline imbalances in our results to address the potential selection bias.

Our collection of patients' baseline characteristics were limited by the usual challenges posed by a health record methodology. For the exposure, patients who did not have archived lung POCUS or any such documentation were assigned to the no POCUS

group. This misclassification may dilute the result so that the results may have potentially limited the observed benefit of lung POCUS.

Because we used the three different reference diagnostic criteria as a reference standard for the final diagnosis depending on discharge status of patients, differential verification bias might be introduced. For the final diagnoses by reviewers, they might have been aware of the POCUS finding and/or interpretations if they were documented in the ED health record by ED physicians archived in Oacis, although they were blinded to the Qpath archiving system for POCUS. However, among 51 reviewed patients for the final diagnoses, there were 11 patients who actually received lung POCUS, but only three of the 11 had documentation about lung POCUS in the ED health records in Oacis. The reviewers were not aware whether the 48 patients actually received lung POCUS. Thus, the effect of this factor should be limited.

We did not account for treatment administered even before arrival to the ED by paramedics, which could have included intravenous fluids, bronchodilators, and diuretics. Therefore, the incidence of unnecessary treatment experienced by patients might be underestimated.

Because we only focused on disease-specific treatments we defined, we could not assess other inappropriate treatments in the ED such as inappropriate fluid administration for patients with acute heart failure. Therefore, our results may underestimate the total incidence of inappropriate treatment administration.

We were able to follow only patients who returned to The Ottawa Hospital or other clinics which sent clinical documents or letters to The Ottawa Hospital for a return visit. Therefore, our results may underestimate the incidence of return visits.

5.6. Clinical Implications

This is the first study to report on the time differences in ED length of stay and ED length of care from the use of lung POCUS for the assessment of heart failure in the ED. Unfortunately, we could not find differences in ED length of stay and ED length of care by using lung POCUS for our study population.

However, we successfully demonstrated that lung POCUS in the ED could shorten the time to appropriate treatment for patients who are suspected of acute heart failure or COPD, accounting for the time-dependent nature of lung POCUS. We found that this potentially faster treatment was especially large if the lung POCUS was performed within 30 minutes in our data.

The 31-minute difference in the time to appropriate treatment between the POCUS and no POCUS group may be clinically important for patients, since faster treatment could provide faster relief of symptoms. According to a previous study, faster administration of diuretics for patients with acute heart failure might be associated with decreased in-hospital mortality. Matsue and colleagues conducted a prospective multi-centre cohort study to evaluate the association between time to diuretics for patients with acute heart failure and in-hospital mortality. The authors found that in-hospital mortality for patients who were treated within 60 minutes were significantly lower than those treated later than 60 minutes (2.3% vs. 6.0% respectively; P=0.002).[70]

It is important to measure and assess the classification performance to show the accuracy before we can interpret the potential clinical benefits of lung POCUS. The classification performance of lung POCUS to identify acute heart failure was better than that of chest X-ray in our data.

Although we did not have the statistical power to find differences in adverse events, it is important to note the point estimates tended to favor the lung POCUS group. Inappropriate ED diagnosis could be reduced by the use of lung POCUS in the ED.

Overall, we were able to demonstrate potential benefits of using lung POCUS, especially faster treatment. This thesis work confirms that lung POCUS can accurately be performed by ED physicians, and provides potentially important information that could significantly decrease the time to administration of appropriate treatment for patients visiting the ED with suspected acute heart failure or COPD.

5.7. Future Research

Since we realized several avoidable factors that could affect our results, further research to find the difference in ED length of stay and ED length of care from the use of lung POCUS should be a prospective study with a larger sample size. The data collection has to be designed properly, including the purpose of lung POCUS. The assessment by lung POCUS should be done earlier, before treatment administration, or before disposition decision making. Our results may help other researchers in emergency medicine calculate more accurate sample size for studies to assess the time-effectiveness of lung POCUS on ED length of stay and ED length of care.

We have demonstrated the possible time to appropriate treatment saved by lung POCUS. To validate our results, prospective studies with a larger sample size and multi-centre involvement are required. Given the study by Matsue, we could confirm the impact of lung POCUS on hospital length of stay and possible survival in future studies.

In order to provide more valid classification performance, a prospective observational study with a single reference standard diagnosis would be appropriate. Further

studies are needed to demonstrate the classification performance of lung POCUS in different settings with different populations, such as community hospitals, outpatient clinics, palliative care centres, or paramedics.

To detect the difference of adverse events rate, much larger studies are required. As the adverse events rate seems to be small, a prospective, multi-centre, observational study with more robust diagnostic criteria for the reference standard would be needed.

5.8. Final Conclusions

Acute heart failure and COPD are common causes of dyspnea in the ED and are sometimes difficult to differentiate. Lung POCUS is not yet a standard assessment tool for the recognition and management of acute heart failure. Although lung POCUS did not appear to decrease ED length of stay, ED length of care, or pre-defined adverse events, we found that lung POCUS resulted in faster administration of disease-specific treatments for acute heart failure and COPD patients. Our results suggest that lung POCUS could improve the management of patients with suspected acute heart failure or COPD in the ED by specifically reducing the time to treatment given its good diagnostic accuracy, however, future research is required to confirm the benefits.

Because this thesis successfully provided new evidence on clinical impact of lung POCUS on time-effectiveness as well as accuracy, it presents important information that can potentially inform treatment strategies. We hope ED physicians can improve their management of dyspneic patients, hospital administrators may increase the availability of US machines in the ED, and researchers can better design future studies to support our evidence. We believe this could help patients, clinicians, and researchers to receive and provide more efficient and patient-oriented care for dyspneic patients.

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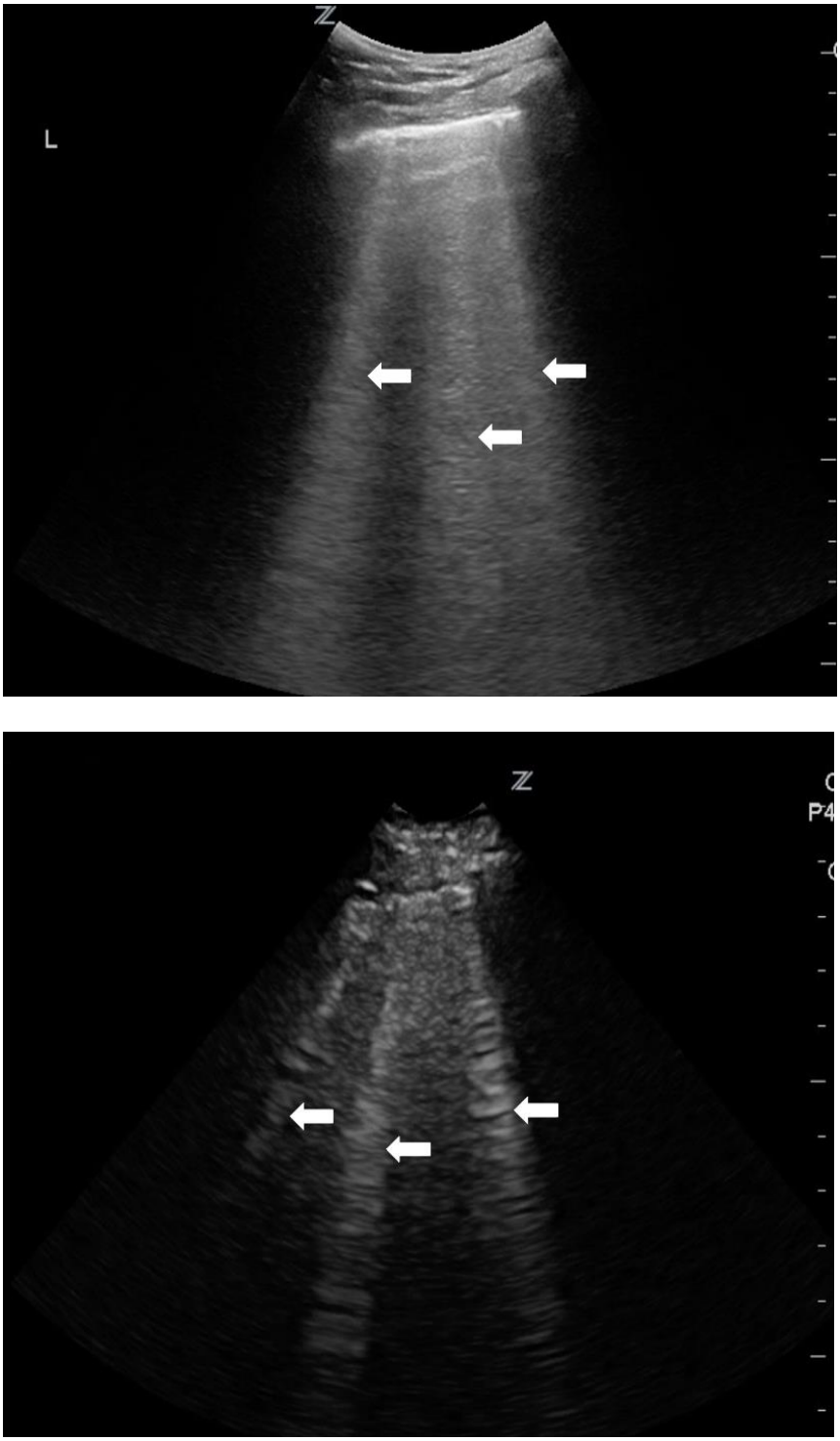
APPENDICES

Appendix A. Examples of B-Lines on Lung POCUS



Multiple B-lines on lung POCUS that arise from the pleural line extending to the bottom of the screen (arrows)

Appendix B. Data Collection Sheet

Case Record Form

Date:_____/_____/_____ Site: O Civic O General Case No.:_____

Arrival Time____:____, Triage Time____:____, Time seen by ED physician ____:____, Cardiology Request ____:____ O N/A

Disposition Time/Date ____:____, ____/____, O Admitted O Home, Patient left ED Time/Date ____:____, ____/____

Chief Complaint: O SOB O Cough, Diagnosis in ED ( ), Physician ( )

Age_____, Sex: O Female O Male, Triage Level: _____, Arrival by EMS: O Yes O No

Temp_____, HR_____, RR_____, BP_____/_____, O2 saturation_____ on RA/O2 ____L/min, GCS _____

Past Medical History: O Yes O No (if yes, check all that apply)

O Heart Failure	O MI/Angina	O Chronic Liver Disease
O Pacemaker	O Peripheral vascular disease	O Chronic Renal Failure
O Atrial fibrillation	O Stroke or TIA	O Intubation for respiratory distress
O Hypertension	O Cancer	O Smoker (current or former)
O Diabetes	O Dementia	O COPD
O Asthma	O Others (_____)	

Medications: Home Oxygen? O Yes O No

Current Cardiac Medications? O Yes O No (if yes, check all that apply)

O ACE inhibitors/ARBs	O Beta Blockers	O Nitrates
O Anti-arrythmics	O Ca Blockers	O Statins
O Warfarin	O Digoxin	O Vasodilators
O NOAC	O Anti-platelets	O Diuretics

Current Respiratory Medications? O Yes O No (if yes, check all that apply)

O Antibiotics	O Inhaled Anticholinergics	O Inhaled Beta-agonists
O Inhaled Steroids	O Oral Steroids	O Methylxanthines
O PDE4 inhibitors		

Current Symptoms: Duration of SOB: _____ hours O N/A

Date: Mar 15, 2017

O Cough O Sputum production O Orthopnea O Other ( )

O Nausea/vomiting O Chest pain O Palpitation

Physical Exams: O Bilateral crackles on auscultation O Bilateral wheezes on auscultation O Peripheral edema

Use of X-ray: O Yes O No positive pulmonary edema?: O Yes O No O N/A

POCUS: O Yes O No Sonographer's Experience: O Attending O Resident; PGY-(_____)

Q-path data sheet filled by Sonographer: O Yes O No

B profile (3 or more b-lines per zone bilaterally): O Positive O Negative O Indeterminate

Pleural Effusion: O Yes O No O Indeterminate O Not Performed

LV function: O Normal/Mild dysfunction (EF = 40 - 70%) O Moderate/Severe dysfunction (EF < 40%)

O Hyperdynamic (EF > 70%) O Indeterminate O Not Performed

POCUS diagnosis: O Acute HF O No acute HF ( ) O Indeterminate

Treatments:

Diuretics:	O Yes	O No	Time (:)
Vasodilators:	O Yes	O No	Time (:)
Emergency dialysis:	O Yes	O No	Time (:)
Beta-agonists:	O Yes	O No	Time (:)
Anticholinergics:	O Yes	O No	Time (:)
Steroids:	O Yes	O No	Time (:)

ED diagnosis: O Acute HF O COPD exacerbation O Other ( )

Disposition: O Discharged home O Admitted O Transferred O Died

Time of POCUS: (:)

Time of disease-specific appropriate treatment: (:)

Final diagnosis: O Acute HF O COPD exacerbation O Other ( )

Return visit within 7 days: O Yes O No

Diagnosis changed: O Yes O No

Date: Mar 15, 2017

Appendix C. Cox Proportional Hazards Regression Model with a Time-Dependent Variable

Cox proportional hazards model without time-dependent covariates can be expressed as the following:

$$h_i(t) = \lambda_0(t)\exp(\beta_1 x_{i1} + \ldots + \beta_k x_{ik})$$

or $$\log h_i(t) = \log \lambda_0(t) + \beta_1 x_{i1} + \ldots + \beta_k x_{ik}$$

where $h_i(t)$ is the estimated hazard for individual i at time t, $\lambda_0(t)$ is the baseline hazard (i.e. the hazard when all the predictors from x_{i1} to x_{ik} are zero), $x_i, \ldots, x_{ik}$ are k variables for the individual i, and $\beta_1, \ldots, \beta_k$ are parameters to be estimated.[65] The ratio of hazards for two individuals i and j can be written as

$$h_i(t)/h_i(t) = \exp\{\beta_1(x_{i1} - x_{j1}) + \ldots + \beta_k(x_{ik} - x_{jk})\}$$

The β coefficients can be calculated with analysing the maximum likelihood estimates. If the variable x_1 is a dichotomous, $\exp(\beta_1)$ is estimated hazard ratio for the variable x_1.

If the variable x_1 is a time-dependent variable, the model can be witten as

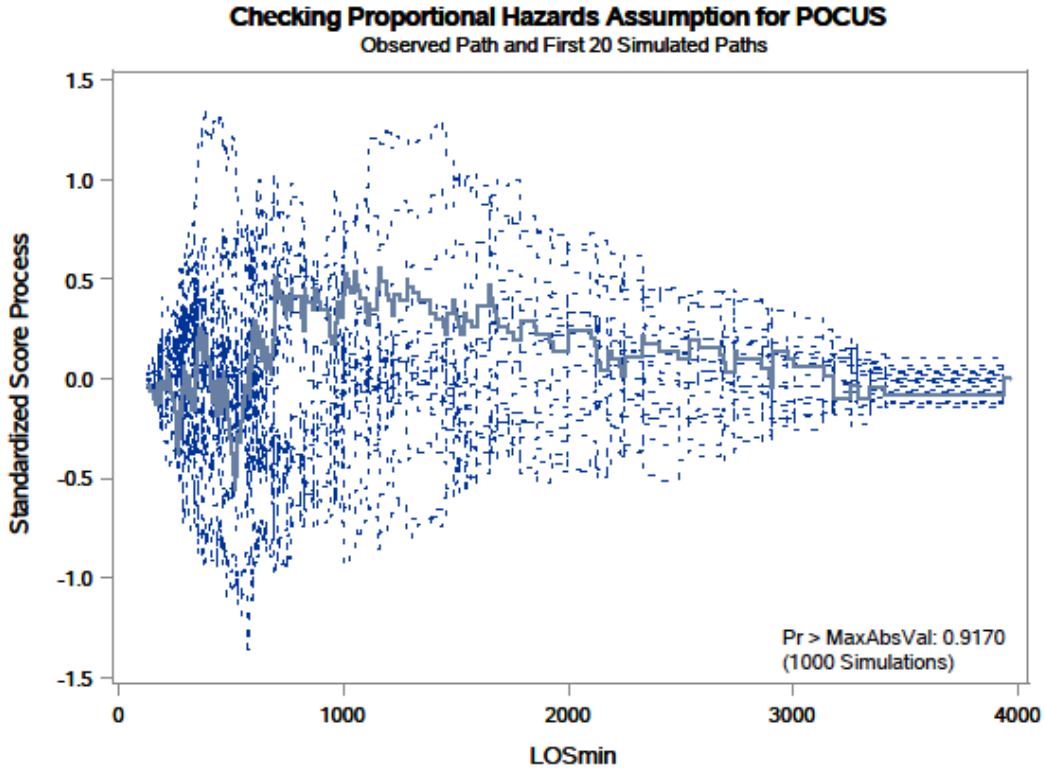
$$h_i(t) = \lambda_0(t)\exp(\beta_1 x_{i1}(t) + \beta_2 x_{i2} + \ldots + \beta_k x_{ik})$$

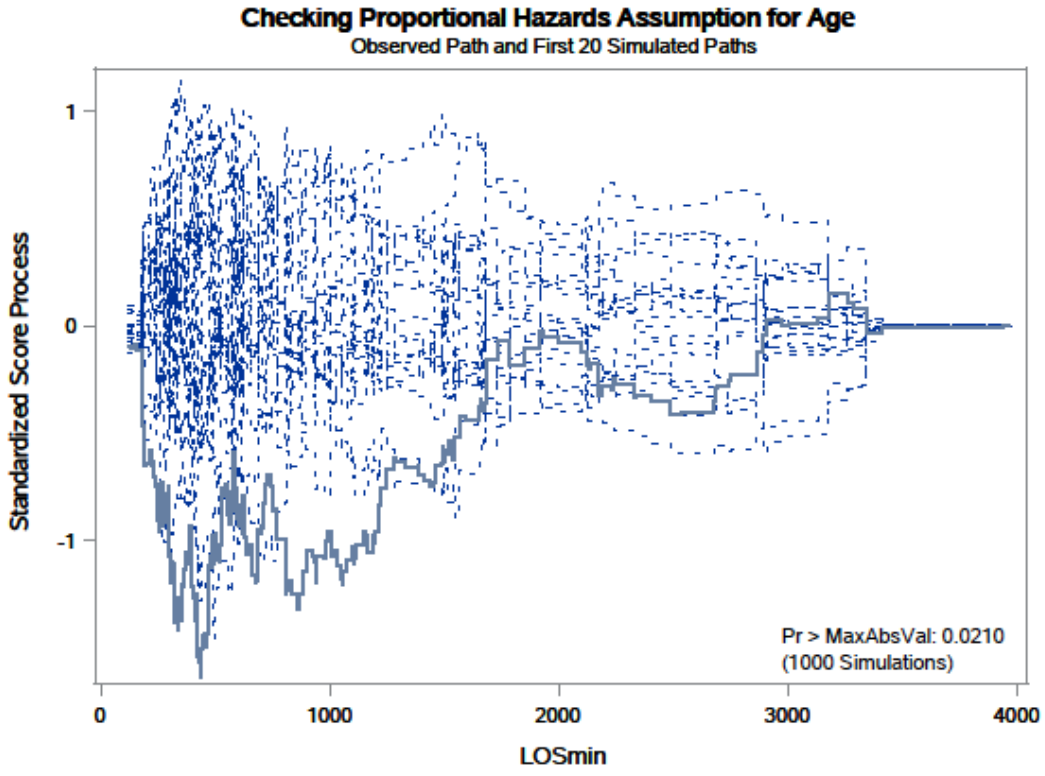
or $$\log h_i(t) = \log \lambda_0(t) + \beta_1 x_{i1}(t) + \beta_2 x_{i2} + \ldots + \beta_k x_{ik}$$

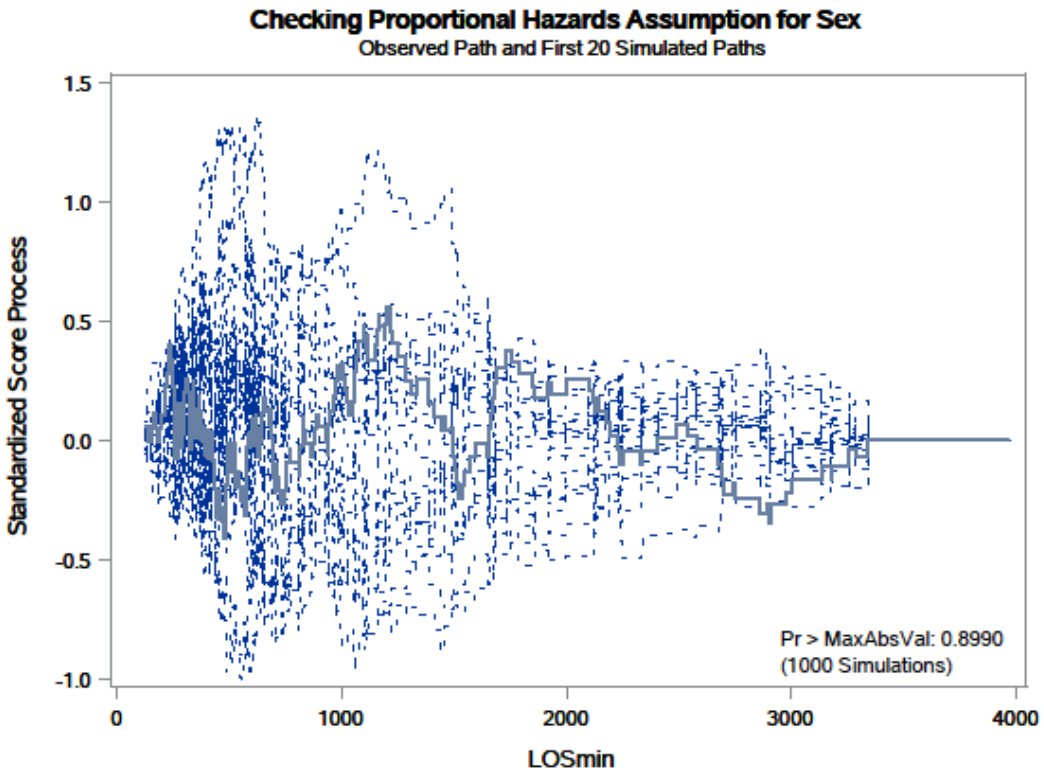
where the value of x_1 changes over time.

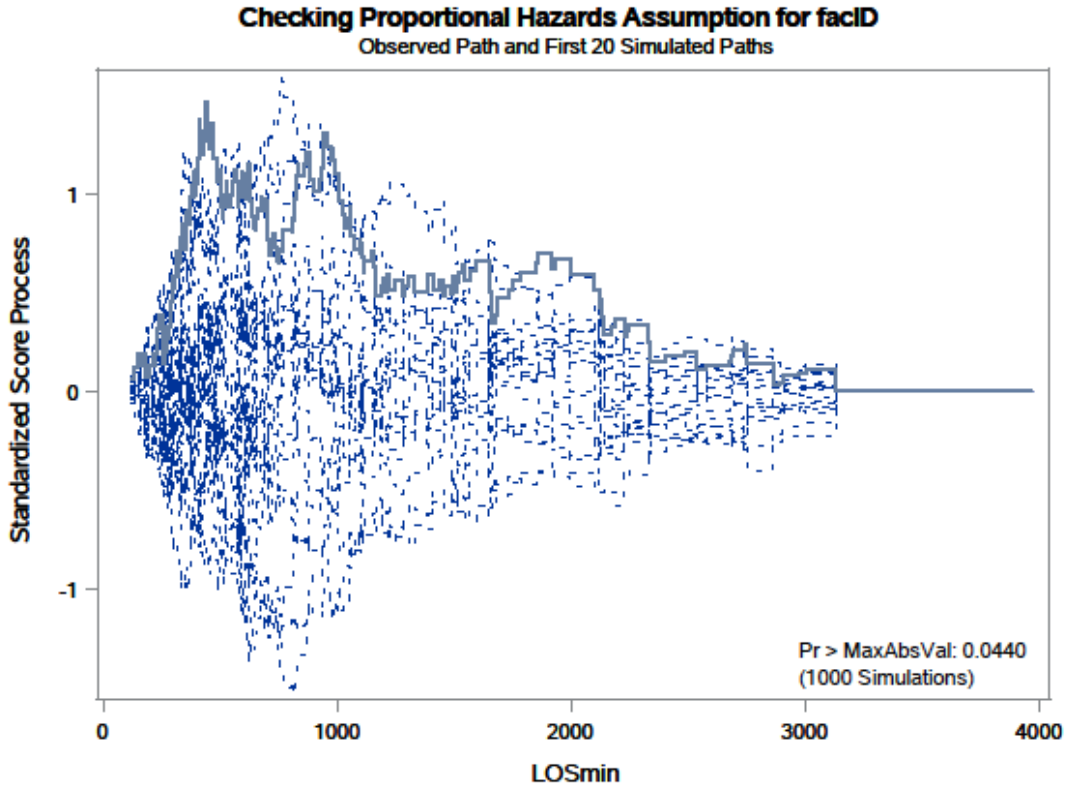
In our study, the status of lung POCUS was a time-dependent variable; the value was 0 if lung POCUS had not been performed, and it turned to 1 after it was performed. Therefore, the hazard function of patients before receiving lung POCUS was the same with the one in the no POCUS group since the status of lung POCUS is always 0 in the no POCUS group. The β coefficients were calculated with analysing the maximum likelihood estimates using SAS software.

Appendix D. Examples of the Graphical Displays of Empirical Score Process for Testing the Proportional Hazard Assumption of Each Covariate Based on Martingale Residuals in Cox Regression Model for ED Length of Stay






Checking Proportional Hazards Assumption for Sex
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.5
1.0
0.5
0.0
-0.5
-1.0
0
1000
2000
3000
4000
LOSmin
Pr > MaxAbsVal: 0.8990
(1000 Simulations)


Checking Proportional Hazards Assumption for facID
Observed Path and First 20 Simulated Paths
Standardized Score Process
1
0
-1
0
1000
2000
3000
4000
LOSmin
Pr > MaxAbsVal: 0.0440
(1000 Simulations)

Appendix E. Adjusted Hazard Ratios of Covariates for POCUS Group Versus No POCUS Group by Time-Dependent Cox Regression Analyses

1. Analysis for ED Length of Stay

Variables	Adjusted HR	95% CI	P value
Registration time to patient left ED time	1.11	0.85 to 1.46	0.44
Age	0.99	0.97 to 1.01	0.22
Sex (male)	1.07	0.84 to 1.35	0.59
Past history of heart failure	0.69	0.52 to 0.92	0.01
Past history of COPD	1.33	0.90 to 1.97	0.16
Past history of heart failure and COPD	0.73	0.52 to 1.03	0.08
Location of ED (Civic campus)	1.12	0.77 to 1.65	0.56
Chief complaint (cough)	0.74	0.35 to 1.54	0.42
Wait time (minute)	1.00	0.99 to 1.001	0.60
Glasgow coma scale	1.14	0.90 to 1.44	0.29
Body temperature	0.88	0.76 to 1.03	0.11
Past history of MI/Angina	1.12	0.87 to 1.43	0.38
Past history of atrial fibrillation	0.86	0.67 to 1.11	0.25
Past history of pacemaker	1.17	0.78 to 1.74	0.45
Taking Ca blocker	0.78	0.61 to 1.00	0.05
Taking digoxin	0.96	0.60 to 1.55	0.87
Symptom of palpitation	0.65	0.37 to 1.15	0.14

HR=hazard ratio; CI=confidence interval; ED=emergency department; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction

2. Analysis for ED Length of Care

Variables	Adjusted HR	95% CI	P value
Physician initial assessment time to disposition decision time	1.05	0.79 to 1.40	0.73
Age	0.97	0.95 to 0.99	0.02
Sex (male)	1.05	0.83 to 1.32	0.71
Past history of heart failure	0.60	0.45 to 0.81	0.001
Past history of COPD	1.31	0.90 to 1.92	0.16
Past history of heart failure and COPD	0.69	0.50 to 0.96	0.03
Location of ED (Civic campus)	0.99	0.77 to 1.26	0.91
Chief complaint (cough)	0.71	0.35 to 1.42	0.33
Wait time (minute)	1.00	1.00 to 1.01	0.04
Glasgow coma scale	1.01	0.57 to 1.79	0.99
Body temperature	0.84	0.72 to 0.97	0.02
Past history of MI/Angina	1.20	0.95 to 1.53	0.13
Past history of atrial fibrillation	0.78	0.60 to 1.01	0.06
Past history of pacemaker	1.30	0.86 to 1.97	0.21
Taking Ca blocker	0.86	0.67 to 1.10	0.22
Taking digoxin	0.91	0.55 to 1.51	0.72
Symptom of palpitation	0.47	0.26 to 0.86	0.01

HR=hazard ratio; CI=confidence interval; ED=emergency department; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction

3. Analysis for Time to Disease-Specific Treatment Administration

Variables	Adjusted HR	95% CI	P value
Physician initial assessment time to disease-specific treatment administration time	1.50	1.05 to 2.15	0.03
Age	1.01	0.99 to 1.03	0.06
Sex (male)	0.83	0.64 to 1.06	0.13
Past history of heart failure	1.22	0.90 to 1.66	0.21
Past history of COPD	1.35	0.86 to 2.14	0.19
Past history of heart failure and COPD	1.23	0.85 to 1.79	0.28
Location of ED (Civic campus)	0.82	0.63 to 1.05	0.12
Chief complaint (cough)	1.61	0.74 to 3.50	0.23
Wait time (minute)	1.00	0.99 to 1.00	0.51
Glasgow coma scale	0.91	0.72 to 1.16	0.44
Body temperature	1.03	0.88 to 1.21	0.72
Past history of MI/Angina	0.82	0.63 to 1.07	0.15
Past history of atrial fibrillation	0.78	0.53 to 1.14	0.19
Past history of pacemaker	0.78	0.51 to 1.19	0.25
Taking Ca blocker	0.98	0.75 to 1.28	0.89
Taking digoxin	1.19	0.70 to 2.02	0.52
Symptom of palpitation	1.20	0.53 to 2.76	0.66

HR=hazard ratio; CI=confidence interval; ED=emergency department; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction