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Summary

Point-of-care ultrasound (POCUS) has emerged as an important diagnostic tool in Emergency Medicine over the past two decades. The term POCUS refers to the sonographic examinations that are performed by clinicians at the bedside of the patient, allowing prompt evaluation and giving useful clinical information in a short time. Common diagnostic applications of POCUS in the ED include the evaluation of the lung, heart, and deep veins, etc. Immediate and accurate diagnosis is crucial to lessen the mortality burden, shorten hospital stay, and to improve the quality of hospital care. POCUS is a non-invasive, safe, cost-effective, radiation-free, and reliable form of bedside imaging that can be used for the diagnosis and the management of several conditions. With all advantages, POCUS in the Emergency Department (ED) has the potential to accelerate the diagnosis for various conditions and to help clinicians to narrow the spectrum of possible differential diagnosis, particularly in urgent conditions requiring rapid treatment decision-making and initiation of the therapy. The use of POCUS in certain diseases is well established and recognized, while the data on its role and clinical usefulness in other conditions like heart failure or syncope are limited and insufficient. The lack of precise standardized diagnostic criteria may contribute to delays in the diagnosis of many conditions because often patients manifest non-specific symptoms that are common for many different diseases. The rapidly growing body of evidence shows the beneficial role of POCUS in comparison to the standard of care, but without indicating the level of efficacy, and because of that POCUS is still not included as an integral part of the standard of care in the guidelines for evaluation of numerous conditions.

In that context, we aim to evaluate the most appropriate way to assess the diagnostic accuracy and the clinical usefulness of POCUS in comparison with other standard tools in different patient populations.

Our findings suggest that the use of POCUS in patients with syncope and in acute dyspnoeic patients presenting to the ED has increased diagnostic accuracy and decreased the rate of misdiagnosed patients in comparison with the standard of care. We also want to point out that LUS appears to be associated with reduced LOS and might accelerate ADHF diagnosis and improve treatment and quality of care in dyspnoeic patients.

With respect to the use of LUS in diagnosing ARDS in dyspnoeic patients when using the Kigali definition, we can observe that the use of LUS may help in simplifying the diagnosis of ARDS and with that may contribute to a more rapid and accurate final diagnosis of ARDS and shorten the waiting times for these patients.

In conclusion, we would like to highlight the substantial role of the use of different modalities of POCUS when added to SOC routine evaluation in assessing patients with acute dyspnoea or syncope and we would like to encourage ED physicians worldwide to incorporate POCUS as an adjunctive step to the SOC in their daily practice. In other words, POCUS is becoming the “fifth pillar” of the bedside diagnosis for many medical conditions and diseases and lately is widely used in everyday medical practice.

Contents

Introduction

1. Ultrasound basics and some technical considerations

Since Hippocrates or better said for more than two millennia the general medical examination consists of its 4 main pillars: inspection, palpation, percussion and auscultation. But in the latest years this concept started to change, getting broader by adding the INSONATION or better known as bedside ultrasound as fifth pillar to the bedside physical examination. By this imaging technique we are allowed to see more completely, more profoundly and more accurately what deviates from the normal wellbeing. The Emergency rooms (ERs) are the places where the larger proportion of the patients have the first contact with the threating physician and are receiving the initial examinations and care. The most of these conditions are life-threatening and urgent conditions which needs to be promptly and accurately diagnose, which was reached by improving the point-of-care testing in the ERs which allowed to lessen the diagnostic time and to timely initiate the proper therapy. Accelerating the time to diagnosis and triage plays a pivotal, essential role in reducing the mortality and morbidity in critically ill patients.

By various studies it was demonstrated that point-of-care testing helps in fulfilling these goals in the ERs, augments the operational efficacy, shorten the length of stay (LOS) and consecutively leads to increased patient satisfaction(1) and better outcomes (reduced mortality and morbidity(2)(3)). One of the most used point-of-care testing tools in Emergency Medicine and ERs is the point-of care ultrasound.

A human being can hear between the range of 20 Hz to 20KHZ. Anything that comes beyond is ultrasonic, and diagnostic ultrasound comes in the range of higher frequencies.

Ultrasound waves are waves that are above the hearing threshold (over 20 KHz). In diagnostics the diagnostic ultrasound range typically are between 1-20 plus MHz. We express the frequency of diagnostic ultrasound in a measure known as millions of Herz (MHz)(4) .

Ultrasound imaging, also called sonography, involves exposing parts of the body to high-frequency sound waves and a picture is produced which mirrors the inside organs of the body. Because ultrasound images are captured in real-time, they can show us the structure and movement of the body internal organs.

Ultrasound machines are equipped with probes that act as transducers for the provided ultrasound waves. By the aid of piezoelectric crystal material, the transducers convers the electricity to ultrasound waves, and after encounters an internal body structure, a return waves is produced and again converted by the transducer in electric signal that the machine recognises and transforms it into a two-dimensional image that allows us to recognize the structure that we evaluate(5) (4).

There are three main probes that we use, that vary by the emitted frequency that results in providing different resolution in diverse areas. There are low frequency probes that we use for cardiac and abdominal ultrasound, because of the better depth of penetration. The curvilinear probe or known as abdominal probe emits frequency of 2-5MHz, which results with greater resolution and allows us to better evaluate deeper structures. The phased array probe or

popularly known as cardiac probe emits frequency of 2.5-5MHz with which provides moderate resolution and fair penetration for deep structures (5).

Opposite of these types of probes are the linear probes that emit high frequencies of 7-13 MHz and basically have much better resolution at a shallower depth and allows us to better observe superficial tissues and structures which makes them suitable for guiding vascular procedures, in evaluation of deep venous thrombosis (DVTs) etc.

When the ultrasound wave encounters a structure from the human body that will reflects the wave, the structure will appear on the ultrasound machine monitor as a bright and white and the term used for it is hyperechoic. Opposite of this case, if the ultrasound wave encounters a structures that does not reflect the wave at all or does reflect but very small amount, we will see the structure on the screen as darker and black and it is termed anechoic or hypoechoic, respectively(6).

There are also few ultrasound modes that give us the possibility to pose a question that is related to flow or some kind of movement like “B” mode (brightness mode), “M”mode (motion mode), colour flow mode and power Doppler mode.

2. Point-of-care ultrasound compared to consultative ultrasound

In conventional practice, the Emergency Medicine (EM) physician use the standard consultative ultrasonography. This means that the frontline physical needs to asks a specialist (e.g. radiologist or cardiologist) to perform the ultrasound examination based on the clinical suspicion. Opposite of these when using point-of-care ultrasound (POCUS) the EM physician handles by himself the whole process of performing POCUS, starting from image acquisition, through image interpretation and can use this information immediately in order to pose the most probable diagnosis. By integrating all the information gained by POCUS with the clinical information gained by the physical examination and the medical history, the EM clinician can rapidly develop a management strategy for the patient. With these it is possible to bypass the delays when using the traditional consultative ultrasound (7). Also another important disadvantage of the use of traditional ultrasound is that the specialists, mostly radiologists that are performing the ultrasound may not know the detailed history of the patient and can miss important clinical information.

3. Point-of-care ultrasound definition

POCUS refers to an all-encompassing term that describes a plead of focused or goal directed ultrasound examinations, performed by the threating physician by the bedside of a patient in order to give answer to the posed specific clinical question (4). The portability and compact size of the newly designed devices for POCUS has enabled us to perform ultrasound in all kinds of settings and locations. We can use it wherever is being taken care of the patient starting from Emergency Room (ER), the ICUs but it could be also a rural remote area, space station or on a cruise ship Its origins take place from the end of the 21 century. In Emergency Medicine the ultrasound has gained on its importance and became an irreplaceable tool for diagnosing numerous conditions. Nowadays POCUS is used in almost every field of Medicine, due to its ability to reduce costs, expedite diagnosis and consecutively to enhance care and patient’s treatments. This comes mainly from the non-ionization image acquisition taking to minimum the traditional harmful radiological exposure, portability, bedside use, prompt evaluation of patient conditions and etc. With the use of POCUS, the time for diagnosis decreases, while the

accuracy increases. Anyhow, the versatile use of POCUS is limited because of the training burden that is required to be gained during the residency and then to maintain and improve these skills. Despite all the numerous advantages of the use of POCUS, still there are some limitations like that it is operator depending or user-depending skill. It was a long journey to come from the large, robust and complex ultrasound machines to come to today's portable, mobile ultrasound machines which have greater resolution, compact and miniature design, with the ability to save images and are "on point of care" available. When moving even forward we have the hand-held devices that probably in the future will be in the pocket of the white coat of almost every physician and be used as an adjust to the physical exam.

There are various studies that prove that POCUS improves patient satisfaction, improves emergency physician efficiency as well as help cost savings. The prove behind tis was seen in many papers. In one study it was seen that as soon as you put your probe on the patient you can automatically improve your chance of being liked by the patient. It was found that patient that had pocus has statistically significant higher satisfaction scores. This is very important for ED that relay on satisfaction surveys. In another study it was found that as LOS in ED decreases, the patient satisfaction increases

When we evaluate patients to the ED we use various tools to help us make the diagnosis including taking medical history of the patient, laboratory analysis and some other ancillary tests. In some cases, we need to order some imaging and the options are X-rays, CT scans, in some facilities MRI and ultrasound. In terms of portability, radiation exposure, reproducibility of the results, quality of the image and cost the ultrasound takes the first place. There are various components of ultrasound including image acquisition that actually means obtaining the images and then interpreting this images and incorporating them into the patient care. The POCUS is immediate and you can correlate it clinically because the patient is physically in front of you and you know what specific question you are trying to answer. Usually the question is dichotomous or yes/no question, that are focused.

4. Point-of-care ultrasound history and development in Emergency Medicine

In 1819 a new medical technology had arrived and it was getting a lot of mix attention and apprehension. The stethoscope which nowadays is the universal symbol of a physician, and which was the revolutionary discovery of Rene Laennec(8), was also denied as a new technology that may bring erroneous results and tended to be restricted (9) . The concept of piezo-electricity was discovered long time ago, in 1880 by Pierre and Jacques Curie and it is considered as main concept on which later on is made the fundament of the ultrasound. In 1915 Paul Langevin invented a hydrophone, which is replacement for today's transducers in order to detect German submarines during World War I under water. Almost 150 years later after the discovery of the stethoscope, as history tends to repeat, a new technology arose. In 1943 the Austrian brothers Karl and Frederick Ducek were the first to use ultrasound as medical diagnostic tool when they attempted to locate brain tumours. This ultrasound actually is not the ultrasound we use today, but it is an A mode or amplitude mode of the ultrasound.

Moving on there were two doctors, Doctor Howry, a radiologist, and doctor Holmes, a nephrologist who pioneered the B-mode of ultrasound in 1950s. At the same time was published the pioneering paper on abdominal pathologies by Ian Donald, who was an

obstetrician, announcing with this the beginnings of the clinical ultrasound (10). The use of the ultrasound in that period was with limited applications, mainly in some experimental settings.

Approximately 20 years later, in the 1970s the ultrasound had entered for clinical routine use. In the '90s the Emergency medicine physicians were between the first ones to acknowledge the utility of bedside ultrasound, which was confirmed by the very first publication on ultrasound use by an EM physician in 1988 (11). The American college of Emergency Physician (ACEP) in 1990 were pioneers in supporting and promoting POCUS by offering the first emergency ultrasound course, and later on have published and continuously updated guidelines for POCUS. The very first position paper referring to emergency ultrasound was published back in 1991 from the Society of Academic Emergency Medicine (12). In the past decades mostly Cardiologist as well as obstetricians have been using POCUS in their practice, and in 1999 the American Medical association passed a resolution 802 that stated that all medical specialties have the right to use ultrasound in accordance with specialty specific practice standards. In 2001 the AIUM created a section for emergency ultrasound, and with these the Emergency medicine has been the leader of POCUS education and research. In 2001 the ACEP published the ultrasound guidelines and they listed seven different applications of POCUS including trauma or the extended fast exam, emergency echocardiography, intrauterine pregnancy evaluation, evaluation for an abdominal aortic aneurism, biliary us, renal us and procedural guidance (12). Later on these guidelines were updated in 2008 and the ACEP added other 4 core applications to the list DVT, soft tissue /musculoskeletal, thoracic, and ocular us. In addition, in 2011 ACEP added some advanced application od pocus in EM that are most used for experienced providers including nerve block, bowel, low GI us, advance echocardiogram, testicular and transcranial us (13).

Over five decades later we have sophisticated us machines with over a hundred applications to diagnose and manage patients.

Ultrasound started as a diagnostic tool in the hands of radiologists. Today, ultrasound is equally used for diagnostic purposes as well as for procedural assistance. The use of ultrasound allows to extend the physical exam by adding it as an adjunct to the basic clinical exam skills. We get a lots if valuable information out of doing the ultrasound.

There other four medical specialties including Critical care, Anaesthesia and etc. that have been catching up the trend. In 2011, in a great paper published in NEJM on the use of POCUS, where is summarized the list of medical specialties as well as the ultrasound application(4). This was a big win which placed the pocus on the map of Medical specialties.

5. Applications of POCUS in Emergency Medicine

POCUS has many applications in numerous medical specialties and in different medical conditions and scenarios. It is mainly divided into three loose categories as diagnostic, procedural (guidance) and screening POCUS. The main applications of POCUS, at least the basics of them can be easily learn at the various stages of training starting from medical student, attendee, but also advance care practitioners, physicians and etc.

The American College of Emergency Physicians (ACEP) policy statement is the most updated, comprehensive and specific guideline for the use of emergency ultrasound. To date there are 11 core applications of Emergency ultrasound and from the existing evidence in the literature

the clinical usefulness of each of them is varying(12). The six primarily established applications are:

1. The Focused Assessment with Sonography for Trauma (FAST) examination
2. abdominal aortic aneurism (AAA)
3. emergency echocardiography
4. pregnancy
5. renal ultrasound and
6. hepatobiliary ultrasound

Later on other additional 5 core applications were added:

1. deep venous thrombosis
2. thoracic ultrasound
3. musculoskeletal ultrasound
4. ocular ultrasound and
5. procedural ultrasound

Examples of the practical use of POCUS assisted/aided assessment in the emergency medicine settings are:

- eFAST – focus sonography assessment for trauma
- BLUE protocol – bedside lung ultrasound in ED
- RADiUS - rapid assessment of dyspnoea
- RUSH - rapid assessment in shock
- FEEL-focused echocardiography in emergency life support for cardiac arrest
- ACES-abdominal and cardiac evaluation in shock

This application of POCUS aid to the basic clinical assessment and may contribute to or have good impact on better clinical-decision making and improve patient outcomes.

6. Evidence on diagnostic accuracy of POCUS across clinical applications in Emergency Medicine

POCUS is performed, interpreted and integrated in order to make diagnosis by the bedside. As mentioned previously, the core applications of POCUS include: the chest, the abdomen, vascular and other procedural guidance, from the eye, through the skin and etc., so it has a wide ray of applications.

The diagnostic application of POCUS is broadly widespread and there is a growing body of evidence that elucidate the accuracy of the use of POCUS.

With the technological advancement the number of newly introduced test, biomarkers or technologies and diagnostic tools is constantly growing. However, we need to carefully access and evaluate the potential new diagnostic tool (in our case the POCUS) in order to avoid the negative consequences on medical care expenditure and patient outcomes(14). The diagnostic accuracy measures inform us about the ability of a newly introduced test to discriminate between and/or to predict disease and health. For this purpose, we use few diagnostic accuracy measures: sensitivity and specificity, positive and negative predictive values (PPV, NPV), the area under the receiver operating characteristic (ROC) curve (AUCs), positive and negative likelihood ratios (LR+, LR-), the diagnostic odds ratio (DOR) and the overall diagnostic accuracy. Predictive values are affected by disease prevalence, but more important to be

remembered is that the disease spectrum may have an impact on all diagnostic accuracy measures. In the further text we will explain in details the diagnostic accuracy measures.

From the existing evidence in the literature we know that POCUS should be included in the new standard of care. We know that it has fewer procedural complications and improved cost of care for example for paracentesis and thoracentesis(15) . Guiding vascular access placement is shown to be more successful and safer (16)(17), and it allows accurate and rapid diagnosis of DVT, the causes of acute respiratory failure, RV dysfunction, undifferentiated shock(4)(18) and etc. Another advantage of the use of POCUS is that it can be quickly performed that is seen in the article of Volpicelli et al.(19) for whole body ultrasonography in patients with undifferentiated shock.

One of the most valuable applications of POCUS is the lung ultrasound. Daniel Lichtenstein by many scientist is considered as the father of POCUS and in his career going back by decades he has worked on publishing scores on the usefulness on the bedside ultrasonography(20). Overwhelming medical research studies advocate for the use of POCUS in acute dyspnoea patients, as well as for patients in cardiopulmonary failure.

POCUS allows us a rapid differentiation between the most frequent diseases which are represent by the dyspnoea as main symptom and lead to directed and focus therapy.

Most efficient and quick diagnostic tool for detection of B lines. Along with the patient medical history and blood analysis, ultrasound may by sufficient in ensuring an accurate diagnosis and treatment. CT and MRI are expensive and time-consuming imaging methods, that can often be omitted.

7. What is clinical utility of POCUS and why is important?

Communicating the benefits of a new test, or in other words its clinical utility, can help the decision making process on how and when to implement the new test. As technology evolve, usually the tests get more accurate. What remains challenging is the impact of a new test/tool on patient management and outcomes. Although these outcomes are difficult to measure, still they are crucial in determining the potentially beneficial role of new diagnostic tools.

The clinical utility of test or tool is related to the added value that the test has for patient care. Simplified a test is useful if its results provide an information that can help the patient management and the providers in the decision making process. In clinical settings it can be improved efficacy in decision making, streamlined clinical work flow, decreased length of stay, improved patient outcomes and reduced costs.

We come to pose the question: How is a new tool shown to have clinical utility? Under ideal conditions, a specific study directed for the patient population of interest is conducted and real world clinical outcomes are measured. Than the clinical data is gathered through different modalities. However, we should be always aware that many factors can influence the clinical outcomes, of which diagnostics can be one. Therefore, it is important that the study population with the integrated new diagnostic device is compared to outcomes that are obtained without the use of the new diagnostic device. From this point of view, it is essential that this studies are well designed, including appropriate powering of the study, in order we can make valid conclusions.

US should be used to enhance clinical skills, not to replace them.

8. Does incorporation of POCUS with current standard-of-care provide added value?

Although POCUS has the potential to change the management and to fasten the diagnosis in many specific groups of patients in the ED, still there are broad plead of conditions in which the potentially beneficial effect of POCUS remains unexplained and unknown. This thesis aims to identify the effect of POCUS in the clinical settings through the example of different patient cohorts with diverse underlying pathologies.

Besides the well-known existing evidence on use of POCUS, the impact and clinical utility of POCUS in EM remains still unknown and unrevealed. With our studies we aimed to demonstrate the potentially beneficial effect of POCUS in different patient population that are presenting in ED. In our studies we used POCUS mostly for diagnostic purposes and we denoted fair diagnostic values. However, the clinical and diagnostic impact of POCUS in ED still needs to investigated and supported by other research projects in order to be incorporated in the clinical practice. Although the most recent evidence testimony the improvement of clinical decision making and better outcomes in emergency care settings with the POCUS as a fifth pillar to the clinical examination, still there remains some uncertainty. Bearing in mind that POCUS a skill that id easy to learn if provided good mentorship and adequate minimal training, more accent and support should be given to the training process for residents in ED. Accurately identifying the underlying reason for patient presentation in ED has significant treatment implications and leads to favourable outcomes.

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Objectives and study hypotheses

The main aim of this thesis was to evaluate the diagnostic accuracy and clinical impact of point-of-care ultrasound integrated approach in comparison with the standard clinical approach in different patient population in Emergency Medicine.

Furthermore, we hypothesise that POCUS-integrated approach could have major beneficial impact on patient outcomes in comparison with the standard of care.

Study I

In the first part of the thesis we evaluated POCUS performance in diagnosing acute decompensated heart failure (ADHF) in acute dyspnoeic patients presenting to the ED. Our primary objective was to estimate and compare the diagnostic accuracy and the clinical usefulness of the lung ultrasound (LUS) integrated approach versus the standard of care (SOC) approach by using different epidemiological measures. With this short report we aimed to give short introduction to the diverse epidemiological measures that could be used to evaluate the diagnostic accuracy and clinical usefulness.

Study II

In the second study we aimed to investigate the impact of lung ultrasound on length of stay (LOS) in acute dyspnoeic patients admitted to the Emergency Department. In order to evaluate this association, we set up a linear regression model with LOS as a dependent variable, and LUS, age, ward of admission, the season of admission, SpO2/FiO2 ratio, and experts' disagreement as independent variables.

Study III

In the third study our main objective was is to evaluate the accuracy of the POCUS-integrated approach in risk stratification of patients with syncope in the ED. We hypothesize that the integrated approach of POCUS with clinical assessment and electrocardiographic (ECG) in patients presenting with syncope at the ED, might lead to a better definition of the short-term risk category for patients presenting for syncope, evaluated through the assessment of the occurrence of short-term serious outcomes.

Study IV

In the fourth study our goal was to estimate the hospital-wide incidence of acute respiratory distress syndrome (ARDS) in hypoxemic patients defined according to Berlin definition and Kigali definition. Also we aimed to describe clinical characteristics and outcomes for these patients.

Study I Measures of diagnostic accuracy and clinical usefulness. Epidemiological methodologies applied to the use of lung ultrasound among heart failure patients.

Abstract

Background
It is still not clear which is the best methods for evaluating accuracy and clinical usefulness of new diagnostic tools.

Objective
To evaluate performances of an integrated diagnostic approach with the lung ultrasound (LUS) in diagnosing acute heart failure using several methodologies.

Methods
We calculated the area under the ROC curve (AUC), Brier score, Youden index, net reclassification index (NRI) and net benefit (NB) for the clinical and the LUS integrated approaches in a subcohort of patients enrolled at Molinette Hospital in a previous multicentre study.

Conclusion
NRI and NB seemed to be more informative for understanding the usefulness of a diagnostic tool.

Introduction

Heart failure (HF) is one of the most relevant problems in developed countries and its incidence is increasing progressively with age (1). HF is defined as clinical syndrome with symptoms and signs that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to eject blood (2).
Acute heart failure is a complex and heterogeneous clinical syndrome defined as the rapid onset or change in symptoms and signs of heart failure requiring immediate medical attention and urgent therapy. It is a leading indication for hospitalization, associated with high short-term (intra-hospital) and long-term (6 to 12 month) mortality (2).
Typical HF symptom is shortness of breath (i.e. dyspnea), which is one of the most common complaints in the Emergency Department (ED), causing over 3 million evaluations/year in the United States (3)(4). It is defined as a subjective experience of breathing difficulty. Dyspnea can have two main etiologies, cardiogenic and non-cardiogenic. The diagnosis of HF based on combination of patient's history, physical examination and traditional diagnostic approach (i.e. chest radiography, electrocardiogram, and dosage of natriuretic peptides) is often difficult, and

a large number of the initial etiological diagnoses made by emergency physicians are modified after further examinations leading to dangerous diagnostic delays.

Lung ultrasound (LUS) is a basic application of point-of-care ultrasound(5). It can be quickly performed bedside and it leads to rapid therapeutic decisions (6).
Multiple vertical artifacts (i.e. B lines) at LUS evaluation have been proposed as a sonographic sign of pulmonary congestion (7). they are a good indicator of alveolar interstitial syndrome, but are not specific for acute HF AHF (8). Combination of sonographic and clinical findings might improve diagnostic accuracy of an acute dyspnea aetiology assessment (6).
The recent guidelines from the European Society of Cardiology (ESC), published in June 2016 (2), do not modify the general approach to patients with suspected AHF. The guidelines propose an integrated approach for the diagnosis of HF that should be based on detailed symptoms history, physical examination and further diagnosis confirmation using additional investigations such as electrocardiogram, chest radiograph, echocardiography and biomarkers such as natriuretic peptides (2). Therefore, the only relevant difference compared to the 2012 ESC guidelines is the recommendation to use natriuretic peptides.
The guidelines mention the LUS without indicating its level of efficacy, but suggesting the use of bedside LUS for evaluation of signs of interstitial oedema and pleural effusion if expertise was available (2).
Several epidemiological methods have been suggested to evaluate accuracy and clinical usefulness of different diagnostic tools, but none of them was demonstrated to perform better than the traditional receiver operating characteristic (ROC) curve, mainly in terms of frequency of use.

Objective

With this study we aimed to evaluate different performances of an integrated diagnostic approach, by implementing clinical assessment in combination with the bedside LUS in differentiating AHF from noncardiogenic causes of acute dyspnoea in the ED.

Materials and methods

We used data of patients enrolled at the "Città della Salute e della Scienza di Torino" University Hospital, which is one of the seven Piedmont hospitals enrolled in an observational cohort [ref] In this cohort the diagnostic accuracy of an integrated approach with LUS was evaluated. After the initial clinical work-up (history, physical examination, electrocardiogram, arterial blood gas analysis), the emergency physician EP in charge was requested to indicate the most likely etiology of patient's dyspnea, expressed as a dichotomous variable (cardiogenic or non-cardiogenic). Chest radiography (CXR) measurements were performed in all patients. After the LUS was performed the same EP was asked to reformulate the most likely diagnosis. As a reference test, two emergency physicians, blinded to LUS results, independently reviewed the entire medical records and indicated the final cause of dyspnea, which was used for the calculation of diagnostic accuracy (in case of disagreement, they reviewed together all data and assigned the most likely final diagnosis)
The ability of a diagnostic procedure to distinguish sick from healthy patients determines its accuracy and diagnostic value.
The accuracy of the diagnostic approaches was expressed as the area under the ROC curve (AUC), Brier scores, Youden index.
The ROC curve, a graphical technique for describing and comparing the accuracy of a diagnostic test, is obtained by plotting the sensitivity of a test on the y axis and 1-specificity on

the x axis for the complete range of decision thresholds (9). The Youden Index is used as a summary measure of the ROC curve because it measures the maximum effectiveness of a diagnostic procedure and enables the selection of an optimal threshold value (cutoff point) at the same time (10).
The Brier Score is a measure used for verifying the accuracy of a probability forecast, which refers to a specific event with binary outcomes. It is the average gap (mean squared difference) between forecast probabilities and the actual outcomes (11).
In order to evaluate the beneficial effects of the diagnostic tests we referred to the clinical usefulness. This concept has been defined ambiguously in evaluation of healthcare. The usefulness of a diagnostic procedure is defined as the degree to which actual use of the corresponding procedure in the healthcare is associated with changing health outcomes, such as preventing death and restoring or maintain health (12).
Two very popular measures that are used to assess the clinical usefulness of a diagnostic test are the net reclassification index (NRI) and the net benefit (NB).
NRI evaluates the improvement in prediction performance gained by adding a new predictor to a set of baseline predictors. It is an index that attempts to quantify how well a new test reclassifies subjects in comparison to the old model (13).
The NB is a decision analytic measure that explicitly incorporates weights for detecting disease (i.e. true positive, TP) and over diagnosing non disease (i.e. false positive, FP) (13)(14). It can be interpreted as the fraction of TP classifications penalized for FP classifications. Net fraction of TP gained by making decisions based on prediction with the diagnostic test/marker/procedure compared to decisions without the diagnostic procedure at a single threshold (e.g. prevalence of disease) is net benefit (NB).

Results

The sub-cohort analyzed in this study consists of 310 patients presented to the ED of the Città della Salute e della Scienza di Torino for acute dyspnea, of whom 152 (49%) patients received a final diagnosis of heart failure. The area under the ROC (AUC) of the clinical evaluation, the integrated approach and CXR was 0.874, 0.974 and 0.774, respectively (Figure 1).
The NRI of the approach integrated with LUS for cardiogenic and non-cardiogenic dyspnea were 12.5 (95% CI: 6.9-18.1) and 7.6 (95% CI: 3.9-12.1), respectively. The NB of the clinical and the integrated valuations varied from 13.1 to 10, respectively with a prevalence of heart failure ranging from 40 to 50%.
The Brier score for the clinical and integrated evaluations were 0.11 and 0.03, respectively.
The results for the Youden index for the clinical diagnosis and the integrated approach was 0.747 and 0.948, respectively (Figure 2).

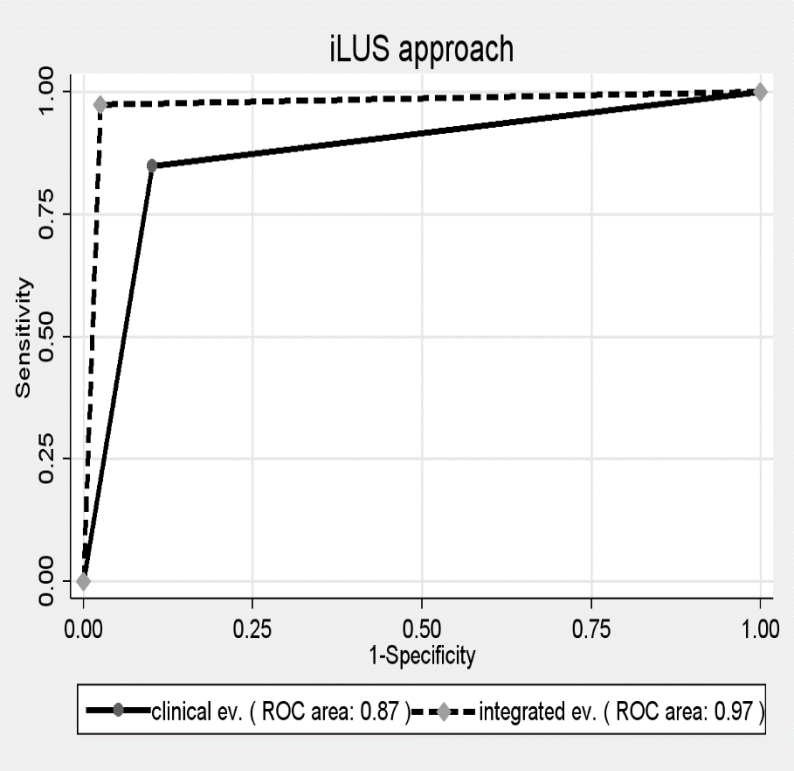

Figure 1. Receiver operating characteristic (ROC) curve comparing accuracy of clinical evaluation and LUS integrated approach.

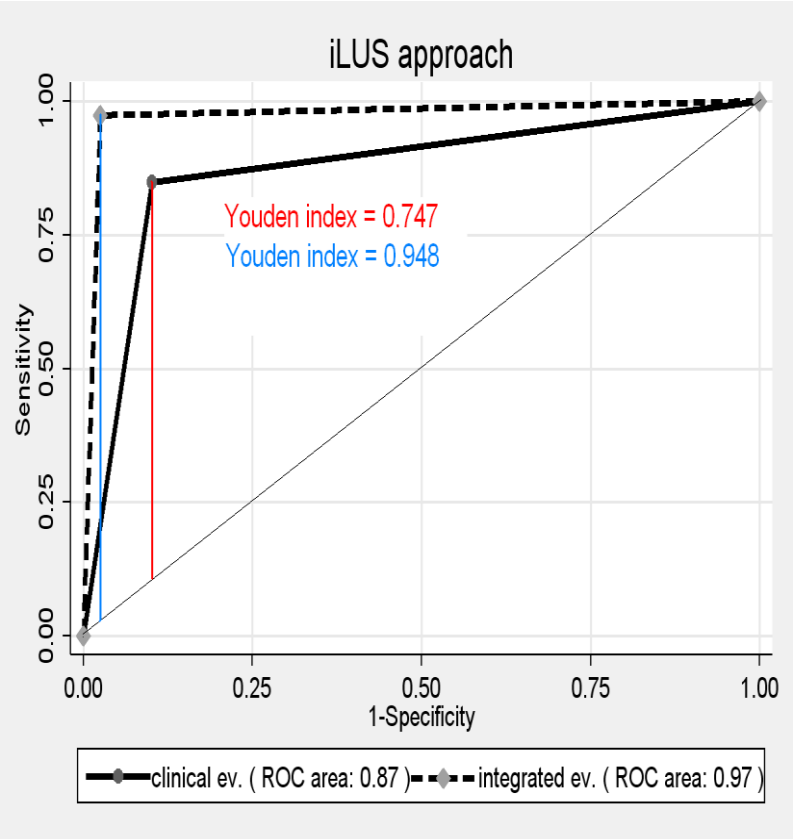

Figure 2. Youden index comparing accuracy between clinical evaluation and LUS integrated evaluation.

Conclusion

The diagnostic accuracy and clinical usefulness of a diagnostic tool could be expressed in several different ways. Although several methods have been proposed, AUC is the most reported measure of accuracy. Despite a widespread use of AUC, NRI and NBs might be more informative, in particular for understanding the usefulness of a diagnostic tool.

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Study II Impact of Lung ultrasound on length of stay in acute dyspnoea patients admitted to the Emergency Department

Abstract

Background: Acute dyspnoea is a frequent complaint in the Emergency department (ED), that can be correlated with different pathologies either from cardiac (acute decompensated heart failure (ADHF)) or pulmonary origin. Lung ultrasound (LUS) is a reliable tool for the assessment of ADHF patients through quantification of the B-lines. This study aims to evaluate the impact of the use of LUS on length of stay (LOS) in patients presenting with acute dyspnoea in the ED.

Methods: We enrolled adult patients with acute dyspnoea admitted to the ED in two university hospitals in Italy. All patients underwent initial clinical evaluation and according to the presumptive underlying aetiology were categorized as ADHF or non-ADHF. Subsequently, patients were randomized to proceed either with LUS or chest radiography (CXR) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) dosage. Linear regression model was used to estimate the impact of a few independent variables on LOS: age, LUS, recovery ward, season, SpO_2/FiO_2 ratio, and experts' disagreement.

Results: A total of 518 patients were included in the analysis. The mean LOS in ED was 432 minutes for recovered and 408 minutes for discharged patients. The use of LUS and the SpO2/FiO2 ratio ($\geq$ 200) were associated with reduced LOS in ED for 88.6 minutes (p=0.05) and 136.4 minutes respectively. Nevertheless, the recovery in general medical ward was associated with an increase in the LOS for 261.4 minutes (p=0.002) as well as the season of the year in which patients were admitted (winter and spring months).

Conclusion: Our study suggests that LUS appears to be associated with reduced LOS and might accurately accelerate ADHF diagnosis and treatment in dyspnoeic patients.

Introduction

Acute onset of breathlessness or dyspnoea is a frequent complaint in the emergency department, which accounts for over three million visits for a year in the US and requires accurate diagnosis and timely treatment (1). It is a common symptom in a myriad of possible underlying cardiopulmonary diagnoses (e.g. acute decompensated heart failure (ADHF), exacerbated chronic obstructive pulmonary disease (COPD), pneumonia, pulmonary oedema) that can potentially be evaluated by ultrasound (2)(3)(4). ADHF is considered as a global pandemic since its number increases with the aging of the population, becoming one of the most relevant public health care issues with prevalence that ranges between 45% and 55% (5)(6). In Italy, there are around 600 000 people with heart failure and it is the leading reason for hospitalization in patients over 65 years as well as worldwide(7)(8). The punctual and correct diagnosis of HF is challenging due to the non-specific symptoms that can be manifested in many other diseases. Emergency departments (EDs) play a significant role because it is known that appropriate diagnosis can reduce the hospital stay, improve patient outcomes, and optimize the use of hospital resources. The lack of standard of care, imprecise diagnostic criteria, and numerous comorbidities in elderly people may contribute to mask important clinical features of ADHF and lead to delays in diagnosis especially in elderly population. Therefore, timely recognition of ADHF in acute dyspnoea patients is crucial. Some previous studies have also shown that prolonged ED length of stay (LOS) is not only a result of the ED crowding but also a potential cause for it (9)(10). The LOS is the total time that patient spends in the ED counting from the first time after arrival in ED (time of triage or registration) until the time of patients discharged from ED and is considered an important measure of the quality of care in the ED(11). It is one of the main indicators for evaluating the performance of hospitals and operational efficacy(12). Prior studies have reported factors that increased LOS like ED overcrowding (13), testing, delays in consultation, certain presenting symptoms, laboratory, disease factors. Furthermore, these can lead to inappropriately transfer to non-specific wards of patients, delayed boarding time, and initiation of treatment, high mortality rate, and negatively affect patient outcomes(10)(14)(15)(16).

The diagnostic limitations of the standard of care (SOC) for diagnosing ADHF have been recognized in some studies that outlined that none of the already included investigations in SOC has sufficient accuracy alone to be considered as “gold standard” for diagnosing ADHF. Several studies have highlighted the possible beneficial role of the use of LUS, as one of the main modalities of point-of-care-ultrasound (POCUS), in the ED in patients with dyspnoea as an additional tool to the SOC(5)(17)(18)(19)(20)(21). LUS is a widely used non-invasive, cost-effective, and radiation-free imaging technique that can accelerate the diagnosis of ADHF. It is an easily obtainable investigation which, available in the most EDs that provides prompt information on lung abnormalities by assessing features of congestion in terms of present B lines and may serve as a differential diagnostic tool in ruling out other pathologies causing acute dyspnoea. The integration of LUS to the SOC can help the ED physicians to narrow the spectrum of potential differential diagnosis and contribute to reducing the length of stay on ED. However, very few data exist on the impact on LUS on waiting times in ED patients.

In that context, we aimed to compare the time metrics, in our case LOS, in patients with ADHF who received lung ultrasound versus standard of care. The primary goal was to assess the impact of LUS on LOS in patients with acute dyspnoea presenting to the ED.

Methods

Our work is based on data from a multicentre, randomized controlled trial (RCT) conducted in two university hospitals, the University hospital "Citta della salute e delle Scienze di Torino" University hospital in Turin and University "Careggi" Hospital in Florence, both in Italy. Previously the institutional boards of the two hospitals approved the study protocol. This trial was conducted following the standards from the Helsinki Declaration for clinical studies involving human subjects and registered on ClinicalTrials.gov (identifier number NCT02105207). Written consent was obtained from all participants in the trial and all data were anonymized.

1. Study population

In our study, we included all patients above 18 years old presenting with acute dyspnoea in the ED. Acute dyspnoea was defined as sudden onset of breathlessness or an increase in the severity of existing, chronic dyspnoea in the previous 48 hours(5). Patients presenting with acute dyspnoea following trauma, patients who were on mechanical ventilation with positive pressure (independently if it was invasively or non-invasively) at the time admitted to the ER for evaluation, psychiatric patients were excluded from the analysis. During the enrolment of the patients with acute dyspnoea was necessarily required the presence of an emergency physician with expertise in LUS (certified according to the criteria of the Italian Society of Emergency Medicine(22)).

2. Study protocol

After the initial evaluation (including detailed medical history, physical examination, electrocardiogram (ECG), and arterial blood gas analysis (ABG)), the responsible physician indicated the possible underlying cause of acute dyspnoea formulating the final diagnosis by dichotomizing it as ADHF or non-ADHF. The patients subsequently were randomized in a 1:1 ratio and allocated in two groups: standard of care group (SOC) or LUS group. SOC group patients received chest X-ray (CXR) and dosage of N-terminal pro-B-type natriuretic peptide (Nt-proBNP), while in the LUS integrated approach group, patients first underwent LUS examination. Thereafter patients were randomized in 1:1 ratio in order to continue the diagnostic work-up.

Subsequently, combining the results of both initial clinical findings and integrated exams, every case was again reclassified and the physician in charge established the final integrated diagnosis (as ADHF or non-ADHF underlying aetiology). Afterwards, the patients in the LUS group underwent CXR and Nt-proBNP dosage following the recommended guidelines(23).

Experienced ED physicians on duty performed the eight-zone scanning LUS as described in the protocol by using a curvilinear probe (5-2 MHz) (24). LUS evaluations were conducted by using ultrasound devices available at time of enrolment in the Emergency Room (Esaote MyLab5, Esaote MyLab30 Gold, Esaote MyLab Alpha, and Philips HD7) equipped with three probes.

LUS examination was performed with patients in a supine or semi-recumbent position(5)(24). According to the approach described in the study protocol, we evaluated LUS group patients for the presence of B lines. B lines are defined as vertical, hyperechoic artefacts that arise from

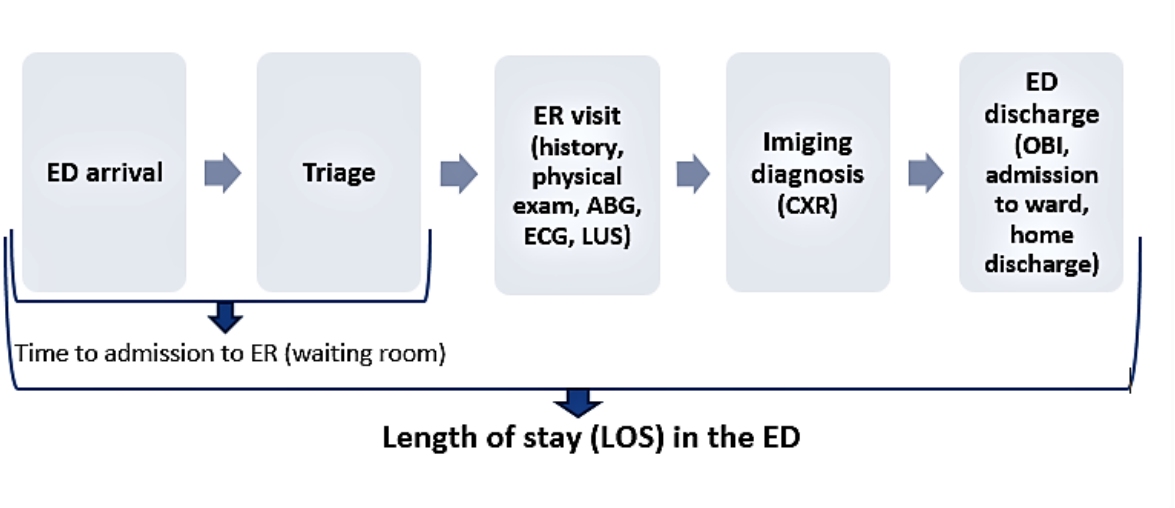
the pleural line, extend to the bottom of the screen without fading and move simultaneously with lung sliding(24). The presence of three or more B-lines in two or more zones bilaterally was considered as indicative for the diffuse interstitial syndrome. We evaluated also the patients for the presence of pleural effusion.

Nt-pro BNP dosage was obtained from peripheral venous blood samples using a commercially available immunoassay in both groups patients. We collected ABG samples on admission in both group patients to obtain partial pressure of oxygen (PaO_2) as an indicator of ADHF severity.

Two intensivists experts after discharge or patients' death, blinded to the previous results, evaluated independently the entire medical records and determined if the main cause for the dyspnoea was ADHF (according to the European Society of Cardiology guidelines for heart failure 2012 (25)). When there was disagreement between the two emergency physicians that evaluated the records, we included a cardiologist that reviewed the entire medical record and posed the final diagnosis (26) .

We collected data on the time of patients' admission and discharge in the ED. Data were extracted from the database and patients' medical records. LOS was measured and also the variables that we believed are related to ED crowding. LOS was measured in minutes and was defined as the total time that the patients spend in ED (Figure 1), from admission (time of registration in the ED) to discharge (hospitalization inward or death).

Figure 1.



The existing literature on variables that could influence the LOS is solid. Based on knowledge from previous research we attempted to select the most suitable subset of independent variables that could potentially affect the LOS, with a major accent on the impact of LUS.

The variables which we took into account and that could potentially influence LOS were: age, LUS, recovery ward (general medicine ward, Emergency medicine, ICU or Short Stay Unit (SSU)), the season in which the patient was admitted in the ED (spring, summer, autumn or winter), SpO_2/FiO_2 ratio (ratio of partial pressure arterial oxygen and the fraction of inspired oxygen), using it as a proxy for severity of respiratory failure (insufficiency) and experts' disagreement. which allowed us to construct a linear regression model in order to explore the impact of few independent variables on LOS.

3. Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as means with standard deviation (SD), or is normally distributed as medians with interquartile ranges (IQR). To assess the differences in the distribution of continuous variables we used Wilcoxon-Mann-Whitney test(27). Our primary outcome was to evaluate the association between LOS and the other independent variable. Therefore, we set up and run a linear regression model with LOS as a dependent variable, and LUS, age, ward of admission, the season of admission, SpO2/FiO2 ratio, and experts' disagreement as independent variables. The results are presented as regression coefficients and 95% CI. The duration of LOS was computed by taking the difference between admission and discharge times from the ED. The coefficient can be interpreted as the average difference in LOS between reference and any other category of a particular variable.

All tests were considered to be statistically significant when p is less than 0.05.

All statistical analyses were performed by using Stata 13.1 version of STATA software (Stata Corp, College Station, TX, USA).

Results

The baseline demographic characteristics of enrolled patients are reported in Table 1 and are in details presented in previously published results that did the analysis on the same data and on same set of patients (5)(26).

We performed analysis on data from a RCT that took place between January 2014 and March 2015 in which adult patients presenting with acute dyspnoea in the ED were enrolled. A total population of 518 patients were included, from whom 260 were randomized in the SOC group and 258 in the LUS group. The median age of the patients was 79 years (IQR 14 years) and the majority were women (243). By reviewing the complete patients' records 43.2% (224) patients received the final diagnosis of ADHF, while 56.8% (294) patients were classified as non-ADHF dyspnoea. In our previous study, we calculated the diagnostic accuracy. Our results showed that the integrated LUS approach had higher accuracy in comparison with the SOC approach, 94.5%, and 87.2% respectively.

The average time that recovered patients spent in the ED was 431 minutes (IQR 708) and 408 minutes (IQR 512.5) for discharged patients.

Patients with ADHF who underwent LUS examination had a shorter LOS for 88 minutes compared with the SOC group. The use of LUS shortens the time to diagnosis and treatment.

In the linear regression model, LOS in the LUS group was significantly reduced compared to the SOC group (coefficient: -88, P=0.05). Patients admitted with SpO2/FiO2 ratio of more than or equal to 200 had a shorter time of stay in the ED, which shows that patients with a milder presentation of respiratory insufficiency were discharged earlier in comparison with patients with severe respiratory insufficiency and require more time for management. The recovery ward, in particular, if the general medicine recovery ward was significantly associated with increased LOS in the ED (coefficient: 226, p value=0.002). The season in which the patient reached the ED, principally if that was winter or springtime was associated with longer LOS. These results are presented in Table 2.

Table 1 Demographic characteristics of enrolled patients, by study arm and final diagnosis

	Study arm		All patients (n = 518)	Final diagnosis	
	LUS arm (n = 258)	SOC arm (n = 260)		ADHF (n = 224)	Non-ADHF (n = 294)
Age, years Median (IQR)	79 (15)	79 (14)	79 (14)	81 (13)	77 (16)
Women, *n* (%)	112 (43.4)	131 (50.4)	241 (46.9)	107 (47.8)	136 (46.3)
Centre, Turin/Florence, *n*	205/53	206/54	411/107	185/39	226/68
Discharge from ED/admission, *n* (%)	19/293 (7.4/92.6)	29/231 (11.2/88.8)	48/518 (9.3/100)	5/219 (2.2/97.8)	43/251 (14.6/85.4)
Length of stay for admitted patients, days, median (IQR)	9 (9)	10 (10)	9 (10)	9 (11)	9 (10)

Table 2 Results from the linear regression model

	Regression coefficient	p-value
Length of stay in ED (minutes)		
Age	2.37	0.179
Use of LUS	-88.00	0.058
Recovery ward (ref. discharge)		
General medicine	226.64	0.002
Emergency medicine	-78.55	0.384
ICU	-10.48	0.963
OBI	46.73	0.713
Season (ref. summer)		
Autumn	43.14	0.666
Winter	145.12	0.085
Spring	81.09	0.357
SpO2/FiO2	-136.42	0.087
Experts disagreement	-122.21	0.104

Discussion

Our study demonstrated that the implementation of point-of-care LUS in the diagnosis in patients with acute dyspnoea admitted to the ED has an impact on LOS by shortening it for 88 minutes in comparison with the SOC. We selected LOS as the outcome variable as it is valuable data that is of common interest as for the patient outcome as for the healthcare system quality assessment. The LOS as a healthcare quality indicator has been studied in a different patient population, for investigating different conditions and in diverse hospital settings. Few previous studies have tried to select the variables that affect LOS in AHF patients. In these studies, it has been demonstrated that elderly age, presence of comorbidities, higher BNP levels, and high heart rate may favour to negative outcomes(28)(29)(30)(31). Anyhow, these variables account only for a small part of LOS. To our knowledge, none other study included LUS in the model, and in our study, it seems to be associated with the LOS. The significance of the association

between LOS and other variables, as reported in clinical literature, in part may be explained by the model that researchers chose to use. Our results were obtained by using a multivariable linear model that controls for already known variables that might influence the LOS in patients with acute dyspnoea and make an improvement in the processing system in hospital ED. Also, this study verifies the successful and reliable use of pocket-sized devices in ED and shows their advantage in terms of accurate and timely diagnosis of ADHF patients. Our findings show that the incorporation of LUS as an adjunctive tool in dyspnoeic patients reduces the time of stay in ED and health care system costs and may contribute to more appropriate, non-delayed tailored patient care.

The acute care of these patients may require a large amount of resources and delayed transfer may lead to increased mortality and lower ED productivity, as outlined in previous study(32)(33). In Italy, according to our knowledge, there does not exist a defined target LOS target for patient presenting to the Emergency Room. There is a "four-hour rule" already introduced in hospitals in the UK and Australia, which means that most patients should leave the ED within 4 h(34)(35). LOS is becoming an issue of serious concern if we implement this rule in the Italian ED hospital setting because our results showed that most of the patients with acute dyspnoea overpassed the threshold of 4h. The average waiting time in most critical periods of the year (winter and spring) in small hospitals in Italy is 6-12 h, while in big hospitals it is between 24 and 72 h.

Hospital shortage of beds has become an actual problem affecting the EDs. Patients with ADHF may have longer boarding for an inpatient bed, especially because most of them need to be admitted in general medicine wards that are usually the most occupied ones. Our findings confirmed it. Also, EDs are usually overcrowded in the colder periods of the year mostly due to respiratory pathologies which may affect LOS for other patients. In our study, we found that acute dyspnoea patients presented to the ED in the winter of spring had prolonged LOS.

This study confirms the findings from previous studies. Our results are in line with the finding from a few other studies, supporting the results of diagnostic superiority for LUS over SOC (24)(36) Our findings are in concordance also with the results from a recent study (37), which described the positive impact of repetitive LUSs on the LOS of patients with heart failure admitted to the internal medicine ward. A novelty of our study is that it is in completely different settings, the ED. Another study(38) reported no differences in LOS associated with the use of LUS in HF patients. The statistically significant 88 min decrease in LOS in our study associated with LUS may partly be a reflection of the differences in ED staffing, different ED organization, and ED to radiology flow process.

Our study has a few important features. First, we confirmed that the LUS group has higher accuracy in comparison with SOC. Second, the physicians were blinded. Third, we demonstrated that by adding LUS to the SOC we can spare 88 minutes in obtaining the right diagnosis in acute dyspnoea patients. These findings may have important clinical and operational relevance for patient outcomes in crowded ED because the time to obtain the right diagnosis is of great importance. Other studies have not seen similar effects. Our study analysed data extracted from hospital records and included data on every single patient rather than some specific patients. The size of the dataset and may be considered as a strength because minor inaccuracy should not importantly influence the obtained results. Another strength is the generalizability of our study which is established by a large number of enrolled patients, from

whom mostly were with advanced age and numerous comorbidities as reported also in previous research studies.

There are several limitations in our study which should also be addressed. First, in the absence of a reliable gold standard and a standardized protocol with precise criteria for the diagnosis of ADHF, we cannot know which model describes more accurately the link between LUS and LOS. Second, our study was limited only to data from our database and our findings need to be validated in other, multiple, independent datasets. However, the cause of increased LOS is multifactorial. Individual patients' characteristics, comorbidities, times that patient spend in waiting for triage or hospital occupancy were not considered in our model because our data analysis were limited mainly to the impact of LUS on LOS. The LOS may be also related to the day of the week of admission/discharge date which we did not take into account, because for example some patients admitted on Friday may experience prolonged stay and not be discharged until Monday due to deficit of senior staff for the weekends. Additionally, one of these is that for investigating the effect on different variables on LOS, the most suitable study design would be observational prospective study, not RCT. The retrospective review of medical records may be dependent upon the accuracy and quality of the original data that was entered in the moment of patients' arrival in the ED.

Conclusions

Our study shows that there is a significant decrease in LOS for acute dyspnoea patients admitted in the ED when the LUS integrated approach is used in comparison with the currently proposed SOC approach.

Based on our findings, we would like to highlight the role of LUS when added to SOC routine evaluation in assessing patients with acute dyspnoea and we are looking forward to encouraging ED physicians worldwide to incorporate LUS in their daily practice. Demonstrating that LUS may have an impact on LOS we believe that our findings may be transferable in EDs and that reducing LOS in acute dyspnoeic patients is an effective strategy also to reduce medical expenses and prevent adverse patient events.

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Study III Comparison between clinical- and POCUS-integrated approach for risk stratification in patients presenting syncope in the Emergency Department

Abstract

Background

Syncope still remains among the most challenging conditions for risk stratification in the Emergency Department, without clear indication when to discharge patients with syncope. The objective was to evaluate the diagnostic accuracy of integrated approach with point-of-care ultrasound (POCUS) in risk stratification of non-high-risk syncope in the ED.

Methods

We conducted a prospective observational study at the University hospital "Città della salute e delle Scienze" between February 2016 and January 2018. All patients above 16 years presenting in the ED for non-high risk syncope were eligible for the study enrolment. After the initial clinical assessment, the responsible physician for the patient was asked to categorize syncope as low or neither high nor low risk. Right after this categorization, the same physician performed POCUS, and made a new risk assessment based of integrated findings from clinical evaluation and POCUS scans. The diagnostic accuracy was estimated in terms of sensitivity (SE) and specificity (SPE) and clinical utility was assessed through the net reclassification index and net benefit that were calculated for clinical and POCUS integrated approach.

Results

A total number of 424 patients with syncope presenting to the ED were eligible, but only 201 patient fulfilled the inclusion criteria and were enrolled to the study. Median age was 64 years (interquartile range, IQR, 30 years).

The SE of the clinical and the POCUS-integrated evaluations was 31.8% (95% confidence interval, CI, 13.9-54.9%) and 40.9% (95% CI 20.7-63.6%), respectively ($p=0.05$), and the SPE was 81% (95% CI 74.5-86.5%) and 92.7% (95% CI 87.9-96.1%), respectively ($p<0.01$).

By using the prevalence of SFSR outcomes in our cohort (10.9%) as a threshold probability, the POCUS-integrated approach would reduce the diagnostic error by 4.5 cases/100 patients.

Conclusion

Our findings suggest that the use of POCUS in patients with syncope in comparison with only clinical work-up has higher accuracy of diagnosis, decreased rate of misdiagnosed and may improve treatment plans and enhance quality of care.

Introduction

1. Definition and epidemiology

Syncope remains one of the most common emergency department entry diagnosis, accounting for more than 3% to 5% of the annual visits(1). Syncope as framework is responsible for around 40% of the total number of hospital admissions in the US with an average hospital stay of 5.5 days, which leads to huge medical burden(2). Still it continues to be quite challenging condition for diagnosis for the front line providers in the ER due to its wide span of presentations, varying from relatively benign to serious life-threatening underlying diseases. That's why the adequate diagnosis and proper risk stratification of syncope patients is from plays enormous role because the expenses associated with management of syncope patients are very high and may have negative economic impact on the health system. The prognosis of syncope patients mostly depends on the underlying cause for the syncope, and accurate and timely identification of it may contribute to better clinical outcome for these patients. The recurrence rate of syncope is around 29 to 35 % for patients with physical trauma which may have negative social impact and worsen-reduce patient's quality of life due to the serious injuries that may arise after any syncopal episode, especially in the elderly(3). The syncope is mostly distributed in the population over 70 (highest incidence rates.

According to the European Society of Cardiology (ESC) guidelines that have been continuously updated(4), syncope id defined as syndrome with reversible and transient loss of consciousness, occurring suddenly with loss of the postural tone, which has complete and spontaneous recovery without any neurological deficiency and without no need of cardioversion(1).

2. Aetiology and classification of syncope

The aetiology of syncope is very complex and heterogeneous group of medical conditions may present as a syncope in the ER. On one side of this span of underlying causes for syncope lay some benign causes that may be self-limiting and that not require hospital admission and extensive clinical work up. On the other side, on contrary, a range of some serious, potentially life threatening disorders are the cause of the rest of the syncope. These patients defined as high risk patient require maximal medical attention and thorough diagnostic evaluation in order to pose – set the most probable diagnosis (usually structural heart diseases) and threat the patient adequately.

Generally, according to the underlying aetiology the syncope's are classified into three big categories that differs between them not only for the pathophysiological mechanisms of occurrence, but also for the clinical characteristics and therapeutically strategies and prognosis(5):

1. Neurally-mediated syncope, also known as reflex syncope
2. Orthostatic hypotension syncope
3. Cardiac syncope, also known as cardiovascular syncope

The identification of the cause of syncope is essential in order to ensure appropriate clinical investigations. One of the most important aims of the diagnostic evaluation is to differentiate the so called "bad syncopes", mostly accounting for cardiac syncopes from the so called "good syncopes" that have more benign underlying causes.

This feature is really crucial, because the prognosis in cardiac syncope is poor, with high reported mortality rates, mainly for patient with New York Heart Association (NYHA) class III or IV(3) (6).

The initial evaluation of syncope patient includes / comprises the following triad of patient history, physical examination and 12-lead ECG(5). However, this initial evaluation has a diagnostic capacity that is between 20 and 50%. Not so rarely in the ED we have patient with syncope from unknown aetiology, whom we should classify in base of the risk they have of sudden death or major cardiac adverse events.

Anyhow the management of a suspected patient with syncope in the ED relies on the response of the following questions:

1. Is it a real syncope?
2. Is there a severe identifiable underlying cause?
3. What is the risk of a severe outcome if the cause remains unknown?

First, the experts suggested three levels of risk stratification (low-, intermediate/indeterminate and high-risk) based on the clinical and electrocardiographically characteristics of the patient presented with syncope in the ED.

Later on, in 2016, a consensus statement for the management of syncope in the Emergency Department (ED) proposed the stratification of patients with syncope in three groups: low-, high-, and the new "neither high nor low" (NHNL) risk that became an integral part of the most recent guidelines of the ESC(1)(7).

The next question that inevitably arises is:

4. Does the patient require admission?

The most recent ESC guidelines suggest direct discharge from the ED for low-risk patients and recommend admission to patients in the high-risk group. Instead of this, patients that are classified at the NHNL risk group (including those at low risk but with comorbidities or with some alarming features(7)) according to ESC guidelines should remain for a closer observation of patient in ED(7).

The risk of patients with syncope depends on to the etiological conditions underlying it. The definitive cause of syncope is often doubtful. Despite of a thorough clinical evaluation in a certain number of patients a clear etiological diagnosis is not determined and these patients are discharged rather with presumptive than with etiological diagnosis (8). Much of the time the exact etiological diagnosis is not determined which underscores the crucial role of assessing patient risk.

The absence of an independent gold standard for the diagnosis of syncope, may lead that patients classified in the NHNL risk group to an unnecessary hospital admission. Several studies have confirmed these data, despite a low incidence of adverse events(9). Also the currently used diagnostic approach for syncope is costly and not so beneficial for the patients(10).

Therefore, the Emergency Department provider approach should be focused on risk stratification of each patient, so it can ease and guide the hospital disposition and management of syncope patients.

In the last two decades, point-of-care ultrasound (POCUS)has revolutionized and has been used in many fields including emergency and critical care medicine, showing increased diagnostic accuracy in several pathological conditions (e.g. acutely decompensated heart failure, trauma, shock(11)(12)).

In this context, we hypothesize that the integrated approach of POCUS with clinical assessment and electrocardiographic (ECG) in patients presenting with syncope at the ED, might lead to a better definition of the short-term risk category for patients presenting for syncope, evaluated through the assessment of the occurrence of short-term serious outcomes (i.e., in the first 30 days after ED evaluation).

The main objective of the present study is to evaluate the accuracy of the POCUS-integrated approach in risk stratification of patients with syncope in the ED.

Methods

The present study is a single centre prospective cohort study conducted in the "Città della Salute e della Scienza di Torino" University hospital in Turin, Italy.

The protocol for the study was approved by the institutional review board of the hospital in Turin and our study was conducted by respecting all the criteria by the Helsinki declaration for clinical research involving human subjects.

All patients with transitory loss of consciousness (TLS), or syncope (main event) as main symptom at the moment of triage, were selected for the study if were fulfilling the following including criteria and were considered eligible:

- ER access for syncope which was defined as complete and transitory loss of consciousness that is not due to traumatic causes, with sudden beginning and short duration, which is characterized by loss of the postural tone and has spontaneous and complete resolution, followed by complete consciousness.
- Age major or equal to 16

We considered the following criteria as exclusion criteria:

- Identification of the underlying cause of the syncopal episode during the initial evaluation (i.e. history, physical exam, and ECG) in the ER
- Patients categorized with high risk conditions before the clinical evaluation
- Patients classified as high-risk patients for short-term serious outcomes
- Those who refused to take part in the study

From the exclusion and inclusion criteria, we can observe that our study population is represented by patients that are classified as low or intermediate risk syncope (NHNL) after the initial evaluation. The reason for these choice are the guidelines from the European Society of Cardiology: 1) for high risk syncope subjects in fact it is highly recommended to be hospitalised in order to proceed with more detailed diagnostic protocol of the syncope. So we considered patients who were discharged (because were considered at low risk) or patients for whom it was not clear weather should be discharged or admitted to hospital (not low, nor high risk, or patients with intermediate risk).

Before we enrolled the patients that were considered eligible for our study, we explained them the details related to our study, and ask them to sign the written informative consent for participation in the study and personal data privacy. It was also possible to refuse the participation in the study by respecting the free will of every patient and it was also possible for every patient that agreed to be part of the study to leave the study in every moment.

All enrolled patient went through a thorough clinical assessment that included a detailed medical history, physical examination including vitals, and ECG. After the initial evaluation, the emergency physician visiting the patient was asked to classify the syncope risk (1) (i.e. clinical approach).

Risk group definitions were based on recommendations in the 2016 ESC consensus on management of syncope in the ED, later on incorporated in the 2018 ESC guidelines update(1)(7).

After the thorough clinical evaluation, the same responsible physician performed POCUS, and a new risk assessment, based on the results of both clinical and sonographic findings, was recorded ("POCUS-integrated" definition).

Basic POCUS examination for patients with syncope included the following scans of i) lungs, for the presence of focal or diffuse B-lines (based on a eight-zone scanning protocol (11)), pleural effusion, and sliding; ii) comparison ultrasound scans(CUS) on femoral and popliteal veins for ruling out deep venous thrombosis; iii) inferior vena cava for examining the volume status; and iv) heart, for a visual assessment of the ejection fraction (dichotomized as normal or reduced), pericardial effusion (dichotomized as absent or present), and of dilatation of right chambers.

To perform the POCUS evaluations, we used an intermediate-size ultrasound device equipped with three probes, linear, convex and phased array (Esaote MyLab5 and MyLab7).

We collected also the time needed to integrate clinical approach results and POCUS results.

In order to assess the frequency of short-term serious outcomes at 30 days after the syncope leading to ED as defined in the San Francisco Syncope Rule (SFSR), every participant was telephonically followed up by the investigators thirty days after the syncope leading to ED presentation, used as a reference in evaluating clinical and POCUS-integrated evaluation accuracy(13)(14).

Statistical analysis

Categorical variables are presented as numbers and percentages, while continuous variables are expressed as means with standard deviation (SD), or if normally distributed as medians with interquartile ranges (IQR). To assess the differences in the distribution of continuous variables between low and NHNL group we used Wilcoxon-Mann-Whitney test.

In order to access and evaluate the diagnostic accuracy of the two approaches, the clinical- and POCUS-integrated evaluation in predicting SFSR outcomes in the first 30 days after ED visit we calculated the sensitivity (SE), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR), and area under the receiver operating characteristic (ROC) curve(15).

For the accuracy comparison between the integrated approach and the clinical approach we used the McNemar test for paired data(16).

Besides the diagnostic accuracy we also created reclassification tables, so we can calculate the clinical utility of the two approaches, by using the net reclassification index (NRI)(17). This index is used to get information on the reclassification power (superiority) of on method in respect to the proposed standard of care method/ or reference test that is used in subjects defines as positive (have an event) or negative (did not experienced any adverse event in the follow up period of 30 days. In other words, the NRI quantifies in how much cases the diagnosis would be modified in virtue of the introduction and the result of using the new test, in our study by adding the echography to the already adopted standard of care for risk stratification in syncope patients.

Additionally, in order to investigate the clinical utility, we also used the decision curve analysis by calculating the net benefit (NB), and decision curve analysis (DCA)(15).

NB quantifies the possible diagnostic gain as the benefit (of a true positive compared to a false negative) minus the harm (of a false positive compared to a true negative) for a given threshold probability of high-risk syncope. We considered statistically significant if p value was minor or equal to 0.5.

Assuming a SPE of approximately 92% of the POCUS-integrated evaluation, a 85% power and a 5% alpha error, we estimated that a sample size of 192 patients would be sufficient to test a 15% SPE difference between clinical only and POCUS-integrated evaluation.

Statistical analyses were conducted using STATA software, version 13.1 (Stata Corporation, College Station, Texas, USA).

Results

A total number of 424 presenting with syncope to the ED starting from February 2016 until January 2018 were evaluated for eligibility. Only 201 patients entered our inclusion criteria and classified as low- and NHNL risk syncope's, were enrolled for the subsequent POCUS evaluation (Figure 1). Median age was 64 years (interquartile range, IQR, 30 years), from whom 110 women (54.7%) and 91 men (45.3%) were enrolled.

Baseline characteristics of patients and ED outcomes are shown in Table 1.

In the first 30-days after the ED evaluation, or in follow-up period, 22 patients experienced 30 SFSR-adverse events (Table 2).

The SE of the clinical and the POCUS-integrated evaluations was 31.8% (95% confidence interval, CI, 13.9-54.9%) and 40.9% (95% CI 20.7-63.6%), respectively (p=0.05), and the SPE was 81% (95% CI 74.5-86.5%) and 92.7% (95% CI 87.9-96.1%), respectively (p<0.01). Positive and negative predictive values were 17.1% (95% CI 7.2-32.1%) and 90.6% (95% CI 85-94.7%) for the clinical evaluation, and 40.9% (95% CI 20.7-63.6%) and 92.7% (95% CI 87.9-96.1%) for the POCUS-integrated evaluation, respectively. Positive and negative likelihood ratios were 1.68 (95% CI 0.85-3.31) and 0.84 (95% CI 0.63-1.13) for the clinical evaluation, and 5.63 (95% CI 2.73-11.6) and 0.64 (95% CI 0.45-0.9) for the POCUS-integrated evaluation.

The ROC curves for the both diagnostic approaches are depicted in Figure 1.

NRI for events and non-events during the follow up was 9.1% and 11.7%, respectively

(Table 3).

By using the prevalence of SFSR events in our cohort (10.9%) as a threshold probability we calculated also the clinical usefulness represented by decision curves – DCI (shown in Figure 3), and we observed that the use of the POCUS-integrated approach would reduce the diagnostic error of the clinical evaluation by 4.5 cases/100 patients.

The median time between clinical and POCUS-integrated approach, measured from the starting time of the clinical evaluation to POCUS performance was 15 minutes (iqr 20 minutes).

Discussion

Our study findings show that the integration of the clinical work-up with POCUS examinations in patients presenting to the ED for non-high-risk syncope might increase the accuracy in predicting the risk of SFSR outcomes and the clinical usefulness.

We observed that although we performed the diagnostic tests recommended by the ESC guidelines, a high percentage (20-40%) of events is still classified as of "unknown origin"(7). In the scientific literature, there are some newly suggested biomarkers (e.g. MMP-7, and TIM-1(18)) and biomarkers indicated for different diseases (e.g. Nt-proBNP and troponin(19)) that have already been assessed in order to decrease this uncertainty, but none of them showed increased clinically-based accuracy in the ED and, consequently, none was accepted for use in the routine clinical practice.

Bedside echo or POCUS is widely performed and used in various medical settings, not only the ED. The use of POCUS may be significantly helpful and with higher accuracy that the standard of care alone in several conditions like acute dyspneic patients with suspicion of acute decompensated heart failure patients(20). However, POCUS should always be considered as an adjunction to the clinical examination, and not as a single imaging test(12).

Our study results suggested that the clinical work-up showed a modest accuracy for correctly identifying high-risk syncope's, similarly to that results already reported in the literature(1)(9). By definition, syncope has mostly a transient cause, that is difficult to identify during the examination.

When adding the POCUS results to the clinical examination, the accuracy of the integrated approach showed an increase of about 10%. Our results indicated that the integrated approach has a high SPE, allowing a good discrimination of high-risk syncope patients from NHNL syncope cases, significantly higher than the one of the clinical approach alone. Despite the fact that the SE of the POCUS-integrated approach was significantly higher than that of the clinical evaluation, we consider this increase not sufficiently high to exclude a possible high-risk event, and therefore less clinically relevant. The adjunction of POCUS augments both SPE and SE with a different clinical impact. The difference in SE does not seem enough to exclude a high-risk syncope in the ED, which may most probably related to the myriad of underlying etiologies of high-risk syncopes, only some of which could be identified during ED or hospital stay, im major cases by ruling them out(1)(8).

In particular, our results also provided evidence to the clinical usefulness of the POCUS-integrated approach using NRI, NB, and DCA (Table 3 and Figure 2).

We defined clinical usefulness as the extension of improvement in health outcomes (e.g., reduced number of SFSR outcomes) compared to the current best option by a diagnostic test. In this study, clinical usefulness is represented by the capability to correctly identify patients with a high risk of short-term adverse events initially classified as low or NHNL risk.

When we stratified based on the clinical work up, we observed an improvement that was obtained by using an approach that theoretically included all syncopes as high risk (figure 2, "treat all" vs "clinical evaluation" curves). The POCUS-integrated approach decreased errors in risk classification in 4.5% of cases compared to the clinical-approach (figure 2, "POCUS-integrated evaluation" curve). The most recent guidelines suggest to discharge or to observe the non high-risk syncope patients, and to admit the others considering the risk of short term malignant outcomes, in order to better define their etiology. In such a situation, a POCUS integrated approach appears to reduce errors in categorizing syncopes regardless of their etiology.

Nevertheless, some of the syncopes might have an electrical etiology that is not possible to be detected by POCUS, but could be presupposed on the basis of history and ECG. Consequently, the usefulness of an integration of POCUS with bedside ultrasound for syncope could be greater in a cohort of patients with a clinically "not-electrical" syncope.

However, our study has some strengths and some limitations.

In the existing scientific literature, several scores have been proposed for the long-term risk assessment after syncope (i.e. OESIL, EGSYS, MK, and SFSR(13)(21)(22)(23)). Anyhow, a recent study suggested that most of these scores overestimate this risk and, also important, appears to be unable to avoid hospitalization of a great proportion of patients after the ED evaluation (12-86%)(24). Our results, which focused on short-term risk assessment, may help in discriminating, among non high-risk patients, those who require admission from those who can be directed to other adequate follow-ups, after discharge from hospital.

An additional specific training of the participant physicians for the POCUS evaluation were not required, except the basic skills for POCUS evaluation that are part of the training curriculum not only in Italy, but also in Europe and in USA.

The short time needed to perform POCUS in our setting may be considered as an advantage of the study. In the hospital, three ultrasound machines were at the same time available for patients' evaluation in the ED (i.e., one for each examination room). However, our results should be confirmed in different-resources hospitals.

One limitation of our study is that in our study we included only patients presenting to the ED with a NLNH risk syncope of unknown etiology, so it cannot be generalized to the whole population of patients presenting with loss of consciousness.

During the enrolment of patients, the presence of a physician able to perform all the POCUS was requested. This condition has not been fulfilled in all shifts in our ED during the study period. As a result of the situation, we probably missed some index events. Despite of this, it is unlikely that this has introduced a selection bias in our cohort, because the presence of staff

physicians in the ED was independent from their skills in bedside ultrasound, suggesting that patients would be randomly missed in every shift.

To conclude, the integration of POCUS with the clinical evaluation of non high-risk syncopes in the ED may increase the accuracy in classifying correctly short-term risk patients and be useful in identifying the patients who need to be hospitalized for monitoring and/or further diagnostic work-up.

	low risk syncopes	neither low nor high risk syncopes
median age (IQR)	61.5 years (31.5)	69 (22)
male/female ratio	0.78	1.05
active smoking habit % (n)	21.4% (28)	21.2% (7)
arterial hypertension % (n)	34.4% (55)	56.1 (23)
diabetes % (n)	10% (16)	9.8% (4)
dislypidemia % (n)	15 % (24)	24.4% (10)
respiratory failure % (n)	1.9% (3)	-
liver failure % (n)	-	4.9% (2)
cerebrovascular disease % (n)	6.3% (10)	14.6% (6)
active cancer % (n)	9.4% (15)	19.5% (8)
chronic renal failure % (n)	1.3 % (2)	7.3% (3)
Vital at the presentation to the ED - median (IQR)		
Clinostatic systolic pressure (mmHg)	126 (30)	120 (35)
Clinostatic diastolic pressure (mmHg)	80 (10)	70 (10)
Temperature (°C)	36°C (0.8)	36°C (0.5)
Pulse rate (bpm)	75.5 (14)	75 (25)
O2 saturation (%)	98% (2)	97% (2)
Admission % (n)	13.8 (22)	19.5 (8)
Discharge % (n)	53.1 (85)	29.3 (12)
Admission after observation % (n)	2.5 (4)	4.9 (2)
Discharge after observation % (n)	30.6 (49)	46.3 (19)

Table 1. Baseline characteristics of enrolled patients, by level of syncope risk at presentation to the ED

SFSR outcomes	low risk syncopes	neither low nor risk syncopes
death, events (%)	2 (1.26%)	1 (2.4%)
acute myocardial infarction, events (%)	none	None
arrhythmia, events (%)	2 (1.3%)	2 (4.9%)
pulmonary embolism, events (%)	1 (0.6%)	None
stroke, events (%)	1 (0.6%)	None
subarachnoid hemorrhage, events (%)	none	None
significant hemorrhage, events (%)	3 (1.9%)	None
any condition causing a return visit to the ED, events (%)	7 (4.4%)	4 (9.8%)
re-admission to hospital, events (%)	2 (1.3%)	1 (2.4%)
aortic dissection, events (%)	none	None
any acute intervention/precedure, events (%)	4 (2.5%)	None
Total, events (%)	22 (13.2%)	8 (19%)

Table 2. List of San Francisco Syncope Rule (SFSR) events during the 30-days follow up period

Patient with low risk syncope		POCUS-integrated		
		low risk syncope	NHNL risk syncope	*Total*
Clinical gestalt	low risk syncope	143	2	*145*
	NHNL risk syncope	23	11	*34*
	Total	*166*	*13*	*179*

Patients with NHNL risk syncope		POCUS integrated		
		low risk syncope	NHNL risk syncope	*Total*
Clinical gestalt	low risk syncope	11	4	*15*
	NHNL risk syncope	2	5	*7*
	Total	*13*	*9*	*22*

Table 3. Reclassification tables for clinical and POCUS-integrated evaluation in predicting San Francisco Syncope rule (SFSR) outcomes. POCUS: point-of-care ultrasound

Figure 1. Area under the ROC curve for the clinical and the POCUS-integrated evaluations (p 0.07 - ROC: receiver operating characteristic curve; POCUS: point-of-care ultrasound)

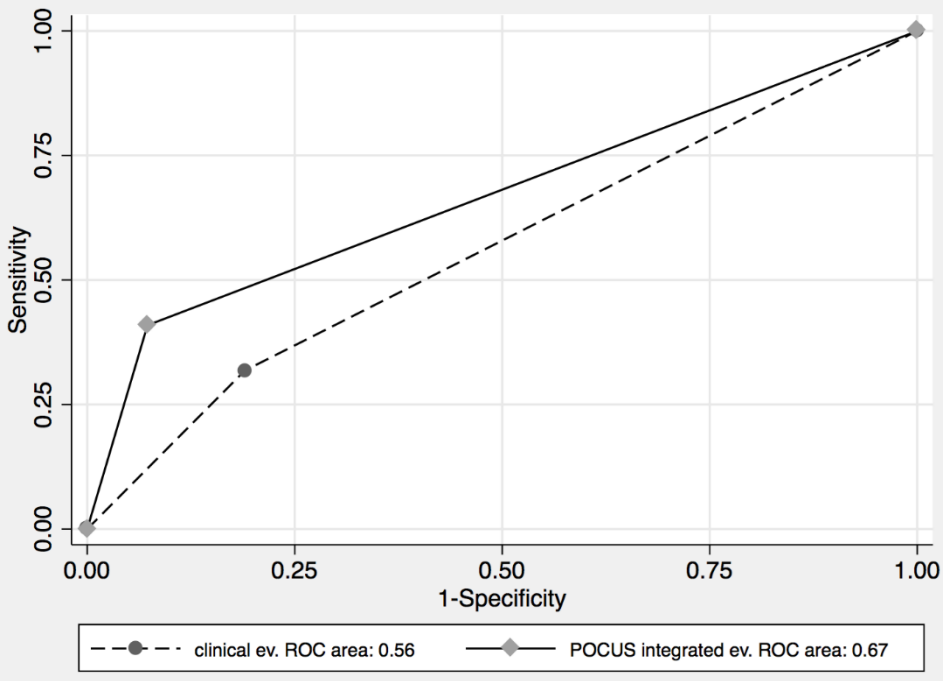
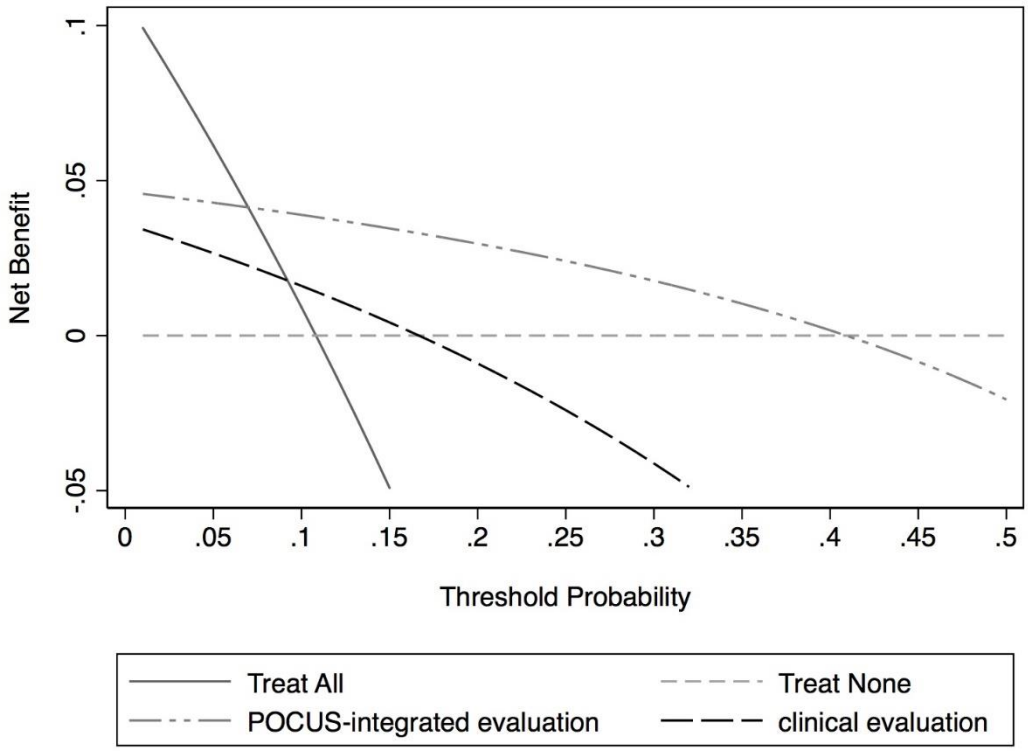


Figure 2. Decision curves for the clinical and the POCUS-integrated evaluations. (POCUS: point-of-care ultrasound)



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Study IV Descriptive clinical characteristics and outcomes in patients with acute respiratory failure enrolled in “NITWA ARDS study”

Abstract

Background

Acute respiratory failure is a frequent syndrome in hospitalized patients and significantly affects their prognosis. Some of these patients suffer from the fearful clinical condition called ARDS (Acute Distress Respiratory Syndrome). The "NITWA ARDS Study" is an observational multicenter prospective cohort study and aims to analyze the incidence, clinical characteristics and outcome of hospitalized patients with acute respiratory failure and to verify whether, in these patients, a diagnostic approach 'simplified', inspired by Kigali's modification of the definition of ARDS according to the Berlin criteria, could contribute to their early recognition in different settings and therefore to better therapeutic implications.

Methods

We conducted a prospective observational study which was part of a multicentre study at the university hospital “Città della Salute e della Scienza” in Turin. We screened every adult patient (older than 18 years) admitted in the study hospital during either of two one-week study periods (summer or winter) for hypoxemia or usage of supplemental oxygen every day in a total range of 7days by using a pulse oximeter. We recruited patients during July 2019 in the summer period, and during February 2020 for the winter period. Patients that had hypoxemia (hypoxemia was defined as oxygen saturation lower than 90%) at the initial assessment or screened patients that developed hypoxemia at some point of the 7 days of follow-up were eligible for enrolment. Data on clinical characteristics of the patients were collected by the use of appropriate forms, while data on oxygenation and the use of supplemental oxygen will be obtained by reviewing medical records (including electronically collected data).

Results

A total number of 872 patients have been screened, of which 146 enrolled according to the inclusion criteria and 91 of these currently have complete data also from an ultrasound point of view. The incidence of ARDS estimated as a diagnosis in discharge (according to the ICD-9-CM) was 3%, while the positivity to the Berlin criterion was 11%, again on a total of 146 patients. The clinical-ultrasound Kigali criterion was achieved instead, on the total of 91 patients with ultrasound data, in 34% of cases for the two-area criterion, in 29% of cases with 4 areas and in 22% of "strict" cases, underlining its greater simplicity of attribution in all settings.

Conclusion

Using the Kigali definition, where lung ultrasound is used together with other clinical parameters in patients with hypoxemia, we observed that the use of LUS may help in "simplifying" the diagnosis of ARDS and with that may contribute to a more rapid and accurate final diagnosis of ARDS and shorten the waiting times for these patients.

Introduction

Respiratory failure (RF) is a clinical syndrome in which the body fails to guarantee gas exchanges and maintain an adequate level of oxygen and/or carbon dioxide in the blood.

In clinical practice we recognize two major types of RF(1):

●Type I or hypoxemic RF, in which only hypoxemia (partial pressure of oxygen (PaO2) <60 mmHg) is present. It is the most common type of RF which can be associated with almost every acute lung illness, which includes fluid filling or collapse of alveolar units. It is determined by a "defect" at the lung or at the level of the cardiovascular system (so-called "lung failure");

●Type II or hypercapnic RF, in which hypoxemia is associated with the presence of hypercapnia (partial pressure of carbon dioxide (PaCO2) >45 mmHg. This form of RF is associated instead by a lack in the respiratory mechanics ("pump failure"), and may represent the natural evolution of an RF type I as respiratory failure takes over.

Hypoxemia is therefore the central parameter for the identification of RF. PaO2 measured at arterial blood gas analysis is however subject to some individual variations, and must be corrected according to some variables such as FiO2 (inspiratory fraction of O2), the age of the patient (according to the formula: Correct PaO2 = 109 – [0.43 x age] mmHg) and position (erect or supine). The severity of hypoxemia is assessed through the P/F ratio (PaO2/FiO2).

There are various pathogenic mechanisms underlying respiratory failure: alterations in diffusion through the alveolar-capillary membrane, alteration of the ventilation/perfusion ratio, shunt and alveolar hypoventilation are some of them. Finally, in order to ensure the homeostasis of the body, gas exchanges at the lung level are important but not sufficient. In fact, the integrity of other parts of the pulmonary system is necessary, because RF can arise from abnormalities also in other components of respiratory tract including the central and peripheral nervous system, airways, respiratory muscles and the chest wall.

Epidemiology and definitions of ARDS

Depending on its onset, respiratory failure can be further divided into acute RF, chronic RF or 'acute on chronic' (or 'chronic exacerbated') RF(2) .

Acute respiratory failure is a frequent and serious cause of hospitalization and / or clinical complication in hospitalized patients. Acute RF is the most frequent cause of admission to intensive care units, and is burdened by a mortality of 35% among patients who require invasive mechanical ventilation. Most of the studies carried out over the years on patients with acute RF have been carried out in the ICU, and this introduces a selection bias with respect to the clinical characteristics and outcomes of all patients with acute RF. A study carried out in the U.S.A. in the years 2001-2009 found that the number of hospital admissions for acute respiratory failure

has progressively increased, but with a simultaneous reduction in in-hospital mortality, regardless of the therapeutic strategy used (MV, NIV or only O2-therapy); the main aetiologies recognized in hospitalized patients diagnosed with acute respiratory failure were pneumonia (40-45%), congestive heart failure (35-39%), COPD (25%), sepsis (13-20%) and ARDS (20%) (2).

While acute respiratory failure has a very heterogeneous underlying aetiology (ranging from pneumonia, to ARDS, to congestive heart failure), chronic respiratory failure with the possibility of exacerbation recognizes Chronic Obstructive Pulmonary Disease as the main causes in the general population - COPD (about 50 %), post-tuberculous pulmonary fibrosis (about 20%), interstitial lung diseases (about 15%), bronchiectasis (about 5%) and other rarer conditions.

However acute Respiratory Distress Syndrome (ARDS) is one of the most feared and life-threatening causes of acute respiratory failure.

Since ARDS cannot be considered as single disease, but more like a distinct type of respiratory failure with acute abnormalities in both lungs, it passed a long way to its todays definition.

It was first defined long time ago, in 1967 in Lancet publication where was emphasized its impact on morbidity and mortality (3)(4).

In the 1980s there was still talk of entities such as "congestive atelectasis", "post-traumatic pulmonary insufficiency" or "shock lung", 'pump lung' after cardiopulmonary bypass and 'Da Nang lung' in soldiers wounded during the Vietnam war. These would probably all have been classified as ARDS today(5).

In 1988, attempts were already made to quantify the severity of this still not fully determined separate nosological entity, which attacked the lungs of acute patients and a system was created with a score from 0 to 4 (Murray Score or LIS).

It is based on PEEP levels, PO2, FIO2, dynamic compliance and degree of radiographic pulmonary infiltration. This score is still used in multiple studies, with therapeutic implications. A score> of 3 is commonly used to quantify the threshold for using the ECMO for example, but it is not able to predict the outcome in the first 24-72 h. When the score is used instead 4-7 days after the onset of the syndrome, scores of 2.5 or higher predict a complicated course that requires prolonged mechanical ventilation (6).

Already at that time the need for greater standardization in the definition was foreseen, for timely diagnostic and therapeutic frameworks.

In 1994 the American European Consensus Conference (AECC) defined ARDS as "an acute inflammatory syndrome manifesting as pulmonary oedema with respiratory failure that cannot be explained by left ventricular failure, but which can coexist with it"(7).

Initially, patients with these characteristics and a PaO2 / FiO2 ratio between 200 and 300 were classified as patients with "acute lung injury" (ALI).

In 2012, the definition of the AECC was re-evaluated and minor alterations were proposed by the European Society of Intensive Care Medicine ARDS Definition Task Force, which lead to posing the fundaments of the famous "Berlin criteria". The Berlin criteria divided the syndrome into mild (PaO_2 / FiO_2 200–300 mmHg), moderate (PaO_2 / FiO_2 100– 200 mmHg), and severe

(PaO_2 / FiO_2 <100) ARDS. These criteria were validated using retrospective cohorts and included patients with mortality ranging from 24% (patients with mild manifestations), up to 48% (severe manifestations) (8).

Until now, a strict application of these definition criteria has been essential, but the different medical settings and the diverse geographic regions in which it is applied do not always allow its application. ARDS is certainly underdiagnosed and there is always spot for improvement in its management. From the data collected from some studies, even when the clinician is given tools to standardize the diagnosis of ARDS, the incidence of underdiagnosed in about 50% of cases.

The main epidemiological data collected so far therefore show a great variability in terms of incidence and mortality (9)(10)(11).

The LUNG-SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (12), conducted in 2014, is among the studies that provides the most epidemiological data on the matter.

According to this study results the ARDS developed in 10.4% of total ICU admissions and in 23.4% of patients who required mechanical ventilation. From these, 30% had mild ARDS, 46.6% moderate and the remaining 23.4% severe ARDS in accordance with the Berlin criteria Furthermore, 67% of patients admitted for acute respiratory failure met the criteria for the diagnosis of ARDS, with early onset (predominantly within the first 48 hours after the development of hypoxemia), but were often underdiagnosed or diagnosed late in clinical evolution, and clinical recognition of the syndrome did not always lead to changes in the therapeutic strategy. Other studies also support this evidence that the vast majority of patients who develop ARDS at any time during their ICU stay already met the criteria in the early days of their respiratory failure(9)(11). The largest incidences are reported in North America, Oceania and Europe, compared with South America, Asia and Africa.

Many data are obviously influenced by various factors, including the number of ICU beds and how they are used (for example, if they also accept patients on non-invasive ventilation, they will probably diagnose more ARDS early due to the possibility of observing patients on PEEP, the way in which intensive care is used also varies between countries with the same socio-economic status). Certainly, countries with more advanced emergency and transport centres have more cases of ARDS related to trauma and burns, as patients survive long enough to develop ARDS. In the same way, however, filtered access to intensive care with a view to activating palliative care programs, especially for the elderly, leads to lower incidences of the latter (9)(11). It is therefore complex to divide geographic factors that can certainly represent biological differences from what is, however, the variation of care services and the possibility of accessing them in various senses.

Analysing other various studies, when expressed as a proportion of 100,000 person-years, the incidence of ARDS varies widely: from 10 in South America (with Brazilian studies with wide variability, from 1.8 to 31) to 18 in Europe, to 34 in Australia, up to 79 in the USA. Also in Europe, substantial differences between north and south were reported, ranging from 10.6 in Finland to 25.5 in Spain.

When classified by macro-region (referring to cases per ICU bed / year) the incidence of ARDS was the highest in Oceania (7.4 cases per ICU bed per year, followed by Europe (6.2), North America (6.0), South America (4.0), while Asia had the lowest incidence (3.5).

Studies examining the impact of ARDS in terms of the proportion of admission to ICUs report a variation from 7.1% to 12.5%.

This also depends on seasonal variations (limit broken down by the Lung SAFE study which takes into account only winter patients in both hemispheres).

Another interesting hypothesis coming from the study by Thille et al.(13) was that the diagnostic criteria have relatively low specificity in the presence of DAD (diffuse alveolar damage), which is considered the pathological trademark of ARDS. DAD was found in autopsy in only 45% of patients who met the Berlin criteria for ARDS at the time of their death. Some patients (14%) therefore did not have lung lesions at the autopsy, suggesting that current criteria could sometimes detect false positives.

Such a difficult measure of incidence certainly presupposes an equally difficult collection of univocal data on mortality, influenced by multiple factors.

In LUNG SAFE, in-hospital mortality has been estimated at 40% worldwide.

In a study using death certificates in the US, it was found that the death rate from ARDS decreased from 1999 to 2013 (codified under the International Classification of Diseases [ICD] -10). Such certificates have a limitation in terms of accuracy, but still the decrease in mortality could reflect a decline in terms of incidence or fatality (14).

Using different ICD-9 codes investigators in Taiwan for example found an increased incidence of ARDS from 1997 to 2011, with fatal cases observed by 57.8% (vs 47.5% of patients with severe ARDS in the LUNG SAFE)(15). There are therefore also problems in the administrative codes themselves, identifying the ARDS, which are often more specific than sensitive and therefore lead to underestimating the cases.

With respect to the mortality most observational studies report that it has not changed in the last 25 years and has remained at around 40% (16)(17).

Finally, the degree of ARDS in a critically ill patient to cause death, in patients with comorbidities and similar risks, has been documented in some, but not all, observational studies. So even today the estimated mortality must be interpreted by asking how many “died from ARDS or with ARDS”.

Further detailed data recording methods would be desirable to produce robust ARDS case identification algorithms.

At a global level, therefore, epidemiological variability remains disarming and between 2015 and 2016 more than 300 indexed articles on ARDS were published, in an attempt to better define it. Especially epidemiological data from low-income countries suggested the urgent need for revision of the current criteria to recognize it early. Each new definition proposed must therefore be evaluated in terms of feasibility, reproducibility as a substitute for a "non-existent gold standard". ARDS is not a syndrome confined to the first world, linked to diagnoses purely related to technological possibilities.

From these assumptions, in 2014, in Rwanda, aroused a study that aimed at revising the complex Berlin criteria conducted by Riviello et al (18). In fact, the incidence of ARDS was measured in the university hospital with the most ventilators in the nation. Before that, the epidemiology of the disease in low-income countries had never been assessed and accurately measured. Certainly here the Berlin criteria were too complex for the available resources in Rwanda. Therefore, subsequently emerged the need for new, simplified criteria, named as Kigali criteria, which envisaged values of SpO2 / FiO2 ⩽315 with an SpO2 ⩽97% and bilateral opacities targeted in ultrasound and radiography when available in order to get the diagnosis pf ARDS in this constrained setting.

To determine the cut off used in these criteria for hypoxemia (SpO2 / FiO2 ⩽315, with an SpO2 ⩽97%), a study by RICE et al was used which showed that SpO2 / FiO2 values of 235 and 315 corresponded to Po2 / fio2 ratio values of 200 and 300, respectively, with good sensitivity and specificity.

These surrogate "Kigali criteria" demonstrated acceptable sensitivity (83%, 95% CI, 52–98), but low specificity (62%, 95% CI, 38–82). However, they brought with them the great advantage of the possibility of removing the mandatory concept of PEEP and precise and monitored quantities of FIO2.

The study was carried out prospectively over 6 weeks. Excluding the cardiogenic cause from the medical record and with echocardiography, when available.

Out of 1046 screened patients, 88 of the 126 hypoxic patients had the SpO2 / FiO2 ratio ⩽315, and 42 (4%) had ARDS according to the Kigali definition. The most common cause of ARDS in this population were infections, major surgery, and trauma. Only 30.9% of patients were admitted to the ICU and all were ventilated. The average age, given the low-income country and the traumatic pathology represented, was on average low (37 years) and mortality was 50%. Importantly, none of these patients would have been identified using the Berlin criteria(11) Table 1.

TABLE 1 American–European Consensus Conference (AECC), Berlin and Kigali criteria for acute respiratory distress syndrome (ARDS)

	AECC definition	Berlin criteria	Kigali modification of Berlin criteria
Timing	Acute onset	Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	P_{aO_2}/F_{iO_2} ⩽200 mmHg (defined as acute lung injury if ⩽300 mmHg)	Mild: P_{aO_2}/F_{iO_2} >200 mmHg but ⩽300 mmHg Moderate: P_{aO_2}/F_{iO_2} >100 mmHg but ⩽200 mmHg Severe: P_{aO_2}/F_{iO_2} ⩽100 mmHg	S_{pO_2}/F_{iO_2} ⩽315
PEEP requirement	None	Minimum 5 cmH_2O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral infiltrates seen on frontal chest radiograph	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or CT	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or ultrasound
Origin of oedema	Pulmonary artery wedge pressure <18 mmHg when measured or no evidence of left atrial hypertension	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)

PEEP: positive end-expiratory pressure; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; CT: computed tomography.

Table 1. Criteria for diagnosing ARDS

Pathophysiology and risk factors

The pathophysiology underlying ARDS is characterized by acute inflammatory lung injury associated with increased pulmonary vascular permeability, increased imbibition of the lung parenchyma, inactivation of the surfactant and collapse of the distal alveoli, with progressive reduction of the alveolar exchange surface. This is initially compensated by hypoxic vasoconstriction that however leads to an alteration of the ventilation-perfusion ratios (19).

Two main conditions that go into differential diagnosis with ARDS are: acute cardiogenic pulmonary oedema and some conditions of the lung parenchyma with gradual progression such as interstitial pneumonia, vasculitis, lymphangitis, which can however evolve in ARDS.

There are two forms of ARDS: primary (or pulmonary, ARDSp) when the noxious agent directly affects the lung parenchyma (for example in case of pneumonia, aspiration of gastric contents, semi-drowning, pulmonary contusions, inhalation of toxins etc.); we speak instead of secondary ARDS (or extrapulmonary, ARDSexp) when the noxious agent acts indirectly on the lungs, through an acute systemic inflammatory reaction (for example in case of severe sepsis, major trauma, cardiopulmonary bypass, massive transfusions, acute pancreatitis etc.).

The distinction between the two types of ARDS is not only speculative: starting from the 1990s some anatomopathological, morphological and pathophysiological characteristics have been identified that often differentiate the two forms, at least in the initial stages and that could influence the therapeutic approach to be used (20)(21)(22)(23) .

In fact, ARDS is a syndrome and not a specific pathology and therefore there are no laboratory investigations or "gold standard" images that define it. Like AKI (acute kidney injury), it is caused by many heterogeneous conditions and consequences.

Multiple predisposing clinical conditions for the development of ARDS have been already described (more than 60 possible causes) and potential causes are continuing to arise since the number of adverse pulmonary reaction to some newly introduced therapies is increasing (24). Anyhow, only a few familiar causes account for the most cases of ARDS. Among the most common known causes associated with ARDS development are the following conditions: sepsis, pneumonia, aspiration, severe trauma, burns, massive transfusion, Transfusion-related acute lung injury (TRALI), lung and hematopoietic stem cell transplantation, drug and alcohol overdose, pancreatitis, fat embolism, some genetic determinants predisposing ARDS and other factors.

In a large study court, the most common underlying causes were pneumonia (35-50%), followed by non-pulmonary sepsis (30%), aspiration pneumonia (10%), and trauma (10%), followed by others risk factors or unidentifiable causes.

However approximately 20% of the patient with ARDS remain with no identifiable cause or risk factor that lead to ARDS.

Other classifications mentioned in the literature are “septic or non-septic ARDS”. ARDS associated with sepsis usually has worse outcomes. While that related to trauma has lower mortality, compared with other types of ARDS (22).

There are still sub-phenotypes of ARDS identified as "hyperinflammatory" or "reactive" which have high mortality rates. The hyperinflammatory variant responds differently to PEEP and

fluid loading, in particular benefiting from the conservative approach (FACTT cohort). In a Dutch cohort of patients, instead, based on four biomarkers (interleukin 6, interferon gamma, angiopoietin and plasminogen activator inhibitor) was made another sub classification into two "non-inflamed" or "reactive" sub-phenotypes, where the latter group is more 'responsive to steroids, to PEEP and fluid loading (benefiting from a conservative approach). There was no difference in mortality, however, between the two groups (12)(24)(25).

The average time to onset of ARDS is usually 48 hours after hospital admission. Therefore, the opportunity for early recognition is limited to a very strict time window. The "late onset" (beyond 48 h of admission to the ICU) ARDS in some studies showed earlier mortality.

Low serum concentrations of vitamin D, which has already known increases the risk of pneumonia and sepsis, since it is involved in the innate immune response, have been hypothesized to predispose for ARDS.

The variant called "TRALI" (Transfusion-related acute lung injury), or associated with multiple transfusions, has long been criticized, questioning its simple immune genesis. In fact, in many of the patients with possible TRALI other more standard risk factors were associated with ARDS (alcohol, smoking, state of shock, fluid balance) (26).

Usually a more severe clinical presentation, a lower P / F ratio, a younger age ("pure ARDS") and the presence of associated pneumonia or pancreatitis make recognition earlier. On the contrary, the absence of risk factors and the presence of concomitant heart failure lead to underdiagnoses of the picture.

Basics of therapy

Early diagnosis is aimed above all for the possibility of timely treatment and therefore reduction of mortality.

From a therapeutic point of view, the revision of the new guidelines essentially involves the analysis of some possibilities, still under study and improvement, but not the subject of the following study. In addition, we will briefly refer to the main modalities of therapies used in patients' with ARDS.

ARDS therapy involves the use of: non-invasive ventilation (the initial use of CPAP is contemplated in mild ARDS) and invasive with the use of PEEP for the purpose of alveolar recruitment, use of protective ventilation paying attention to acidosis (Tidal volume <6 ml / kg for ideal weight), plateau pressure <30 cmH2O, use of neuromuscular blockers, prone position for at least 12 h per day in patients with at least moderate ARDS, corticosteroids (to be used in the first 14 days), use of ECMO, restriction of fluid administration.

High-frequency oscillation ventilation (HFOV) is currently considered ineffective or deleterious. The use of nitric oxide remains still an argument for many discussions.

Preventive pharmacological approaches such as the use of anti-inflammatory drugs such as aspirin or statins with immunomodulation effects initially seemed promising, but their beneficial role was not confirmed in subsequent randomized studies.

Vitamin D deficiency, on the other hand, is shown, as already explained, to be associated with worse outcomes.

Radiological techniques and ARDS

The detection of pathological alterations by the use of instrumental investigations plays a fundamental role in the diagnosis of ARDS, also representing one of the Berlin criteria. Typically, ARDS is characterized by the radiographic evidence (the first examination historically used in this regard) of bilateral parenchymal infiltrates, inhomogeneous and asymmetrically disposed, with an inflammatory-exudative aspect, with no evidence of cardiogenic pulmonary oedema. It is evident that this instrumental finding is in itself highly non-specific, as it is common to a range of pathological pictures with common lung involvement (primarily cardiogenic pulmonary oedema, which is more symmetrical and homogeneous). Therefore, the instrumental findings must be always correlated and integrated with the remaining clinical and oxygenation parameters.

However, chest x-ray remains a rapid, repeatable and available examination in most contexts (Figure 1).

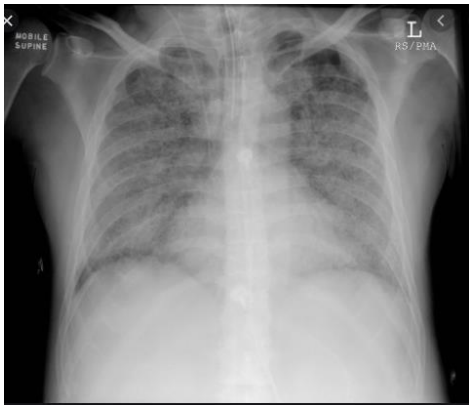


Figure 1. Chest x-ray in ARDS patient

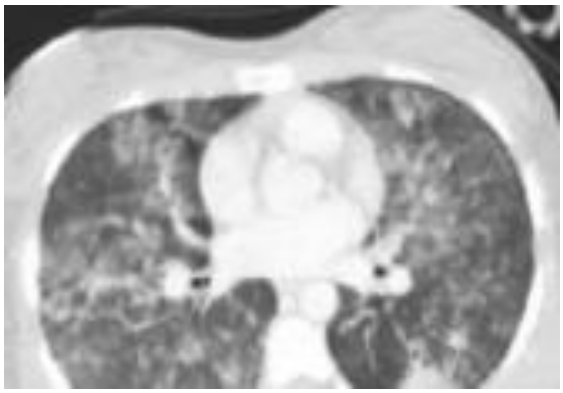


Figure 2. CT scan in ARDS patient

Chest computed tomography (CT) provides more specific information when needed and if available. It therefore represents the gold standard imaging technique in the context of this pathology as well. However, still the main disadvantages of CT are the need to transport the patient out of the intensive care unit (ICU) and exposure to higher doses of radiation (27)

In the context of ARDS, the main alterations detected are the so called "white lung", ground glass opacity (GGO), dense opacity with "patchy" distribution, reticular opacities and bronchial and cystic dilations. Chest CT, in addition to assisting in the diagnostic process of ARDS with complex X-ray picture, has additional roles linked to the greater definition of the examination: it contributes in fact to the etiological diagnosis (pulmonary versus extra pulmonary pathological process), describes the real extent of the pulmonary damage, quantifies atelectatic / normoareate / hyperinflate parenchymal areas. Thanks to this latter potential, over time CT has assumed a fundamental role in the optimization of mechanical ventilation, and became fundamental therapeutic tool in the ARDS, for example for evaluating the effectiveness of alveolar recruitment and pronation manoeuvres, with the possibility to reveal the most affected lung portions by ARDS (Figure 2).

More recently, another imaging method has taken place in the diagnosis of ARDS and that is the lung ultrasound.

A growing body of evidence is constantly emerging in the scientific literature in order to reveal the power of diagnostic accuracy of lung ultrasound.

A prospective observational study carried out in university intensive care and radiology centres calculated the degree of agreement between CT and lung ultrasound performed on 6 screenings in intubated and sedated patients with ARDS diagnosed according to the Berlin criteria. The sensitivity and specificity of ultrasound in this case ranged from 82.7% to 92.3% and from 90.2% to 98.6% respectively, thus proving to be accurate and reproducible. The diagnostic accuracy of ultrasound was also much higher when patterns that did not reach the pleural line were excluded(27).

Another observational retrospective study conducted in ICU that took place between 2014 and 2017 compared the Berlin criterion with radiological imaging (RX) with the Berlin criterion with ultrasound imaging, those who met both definitions had higher mortality.

The ultrasound approach showed a PVP of 0.66 (positive predictive value, 95% confidence interval 0.59-0.72) and a NPV of 0.71 (0.65-0.77).

Both methods have been correlated with mortality, however there is the possibility of loss of cases, which implies that for the diagnosis the two methods may remain complementary(28).

Another study also highlighted the possibility of monitoring and follow-up by ultrasound(29). The study also conducted in intensive care in patients with ARDS showed how the ultrasound performed on 12 projections (with calculation of a parenchymal re-aeration score) correlated with the recruitment performed through increasing PEEP values and also with the increase in pO2 (data not present in other studies in this regard). An important aspect, however, is that it could not correlate with the degree of lung hyperinflation, not distinguishing the normal lung from the latter state.

In the context of ARDS, therefore, thoracic ultrasound has been the subject of study, and is currently applied in the clinical management of affected patients, but there is still no standardized method (for example concerning the number of areas and reporting)(30)(31).

Ultrasound has a number of advantages over traditional radiological methods: it is easily available in any type of healthcare setting, as it is cheaper and more easily transportable and can be carried out in bed and interpreted in real time or afterwards; it does not use ionizing radiation and is therefore safe for the patient and for the operators, it is easily and quickly executable and repeatable whenever a modification of the finding is expected, for example in the therapeutic follow-up; the imaging is "goal-directed", having the ability to focus the examination on the areas of interest and on the search for suspected alterations based on the clinical presentation; the acquisition of ultrasound images can be carried out by any healthcare professional after adequate training. Special training methods were developed, which showed that the learning curve is usually rapid (about 25 hours).

Disadvantages of this method can be the dependence on the operator, the patient's habit and collaboration, the presence of surfaces (e.g. dressings) that do not allow the passage of ultrasounds and the cardiac shadow that often hinders the correct exploration of some lung areas, the inability to explore areas not in contact with the pleural line and etc.

General ultrasound introduction

In summary, ultrasounds propagate in the human body according to straight trajectories, until they meet a boundary surface between structures with different acoustic impedance. In this case, some waves are reflected back towards the transducer (allowing the generation of the ultrasound image in relation to the distance / time from the boundary surface and the intensity of the reflection) while other waves are absorbed by the tissue. Therefore, two main types of interaction are generated: reflection (whose intensity is directly proportional to the difference in acoustic impedance between the two contiguous tissues) and attenuation, i.e. a gradual loss of intensity due to absorption and diffusion, whose entity depends on the conducting medium (maximum within the air and bone).

Consequently, in the normal lung, the ultrasound waves are almost completely reflected at the interface between the visceral pleura and the lung parenchyma, and the remaining waves that cross the interface are almost immediately absorbed. For a long time, it was believed that these characteristics made it impossible to evaluate lung contents through ultrasound, but in the last 20 years a new approach to the method, based on the interpretation of images in relation to the underlying physical mechanisms, has revolutionized this technique use. In consideration of the unique physical properties of the lung, thoracic ultrasound requires the systematic analysis of both anatomical (for example pleural line and consolidated parenchyma) and non-anatomical (represented by the artefacts) images. In an ultrasound scan where the probe is positioned perpendicular to the chest wall, the first layers visualized will be the subcutaneous tissues and intercostal muscles, and, deeper, the outer surface of the ribs with posterior acoustic shadow. The ultrasound image of the chest is represented by a succession of layers. The skin surface (echogenic), the subcutis (with variable echogenicity), the muscular fascia and the muscular planes and finally the ribs with the intercostal muscles and the pleural surface. The ribs (costa) reflect much of the ultrasound emitted and therefore the image that is created below it is a shadow cone ("bat sign"). The pleural line is not static, but dynamic, and is characterized by two main movements: the "pleural sliding", generated by the sliding, during breathing, of the visceral pleura over the parietal pleura, and the "pleural pulse", given by transmission of cardiac contractions to the pleura through the lung. Below the pleural line, horizontal hyperechoic lines will be displayed, regularly positioned at an interval that is a multiple of the distance between the ultrasound probe and the pleural line. These lines are called "A lines" and are reverberation artefacts generated by the strong reflecting power of the pleural line. Actually, the “A lines” are a physiological finding in the normal lung. (Figure 3).

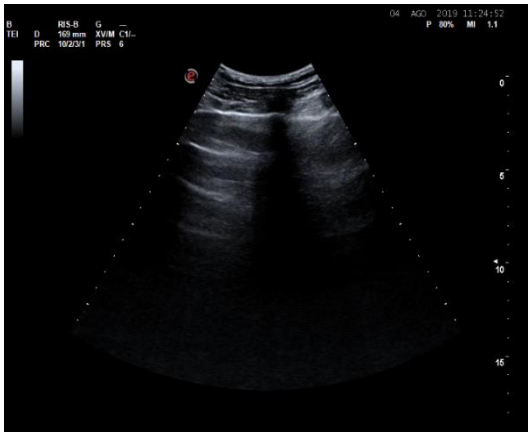


Figure 3. Pattern A: only horizontal A lines can be observed (artefact of normal occurrence in the normo-ventilated lung).

In other cases, instead, vertical lines originating from the pleural line and moving together with the pleural slide are visualized. These are the so called "B lines" and are believed to represent areas of focal density increase in the lung parenchyma (e.g. interlobular septa) (Figure 4).

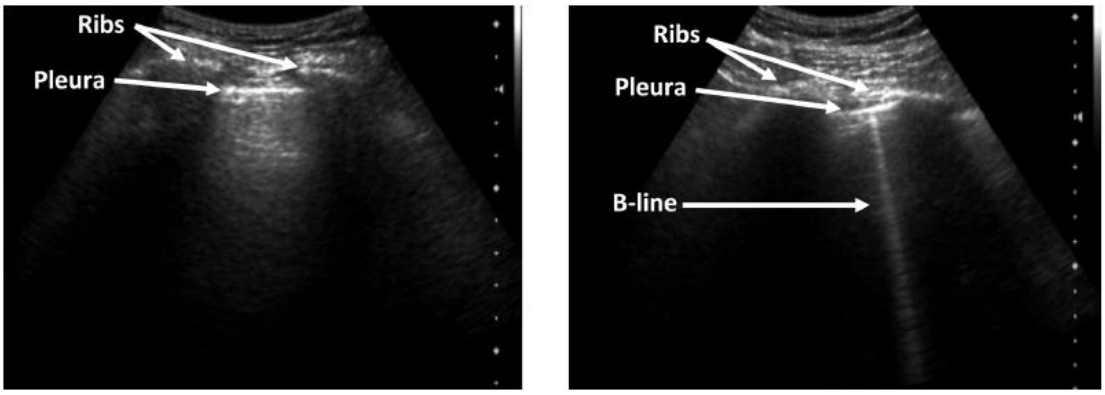


Figure 4. Ultrasound appearance of the ribs, pleural line and B lines.

Other significant findings in pulmonary ultrasound semeiotics are the presence of pleural effusion and pulmonary consolidation (Figures 5 and 6).

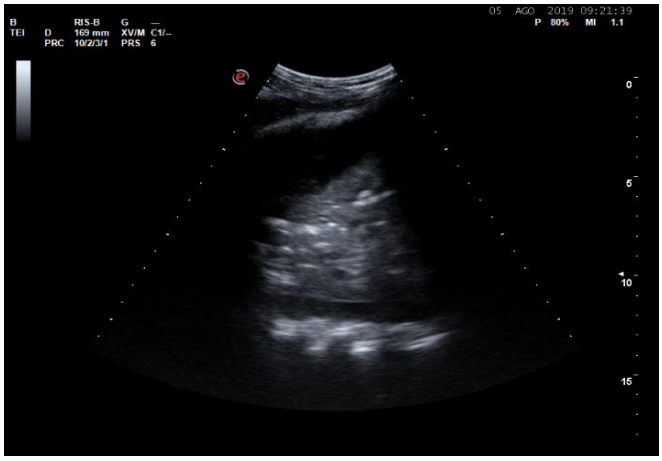


Figure 5. Pattern C: big consolidation in the lung parenchyma.

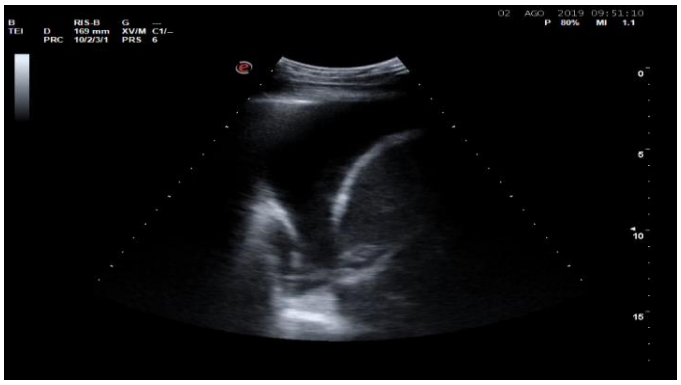


Figure 6. Pleural effusion: liquid (anechoic) present between the diaphragmatic margin and the lung parenchyma.

Therefore, it appears evident the potential that the ultrasound method through its semeiotics could have in the diagnostic and therapeutic process of multiple lung diseases and determine the degree of parenchymal aeration.

In-depth "pattern B"

In 1997 Lichtenstein observed, after random and pioneering reports, that the lung affected by interstitial pathology (mainly oedema) showed characteristic ultrasound images that were described as "comet tails" and later renamed B Lines or "ring down "(32).

The B lines are vertical, hyperechoic artefacts that originate from the pleural line, with a narrower base in the terminal portion, filling the entire width of the screen with the same signal intensity from start to finish and masking the A lines. By definition, they move synchronously with lung-sliding. The precise anatomical-physical basis of the formation of these artefacts is not fully known(33). The B lines are thought to be generated by a phenomenon called reverberation, which is an acoustic phenomenon linked to the reflection of sound by an obstacle placed in front of the sound source. They originate from strongly impeding focus in the pleural and immediately subpleural areas. In the case of oedema, in fact, there is a large difference in acoustic impedance that is produced between the alveolar air and the pulmonary interlobular septa thickened by the liquid(33)(34).

They can therefore be present when different tissue interfaces come into contact (such as lung with air and liquid, lung and diaphragm or intestinal wall and lumen filled with air) or in the presence of foreign bodies (especially if metal). The equipment interprets these repeated echoes (multiple reflections) with an elongated image, which runs through the screen.

Therefore, while the complete alveolar flooding and the elimination of air in the lobules would constitute real ultrasound images (the thickening), the partial aeration of lobules with thickened and imbibed septa would generate vertical reverberations due to resonance phenomena. However, it is also possible that pulmonary lobules with thickened inter- and intra-lobular septa and with partially flooded alveoli behave like microbubbles in a fluid environment, such as to generate resonance phenomena and therefore produce much more concentrated vertical projection images, up to their confluence(32).

These artefacts would have a similar clinical significance to the visualization of Kerley's B lines in chest radiographs of patients with interstitial oedema.

The B lines are considered pathological only in the event that they extend from the pleural line to the bottom of the screen without fading and if numerous (more than three to report the explored area as positive): in this case they indicate an area of increased pulmonary parenchyma density with reduced aeration (as in pulmonary oedema, accumulation of fibrotic tissue, blood, lipids, pus or proteins). (Figure 7) (35).

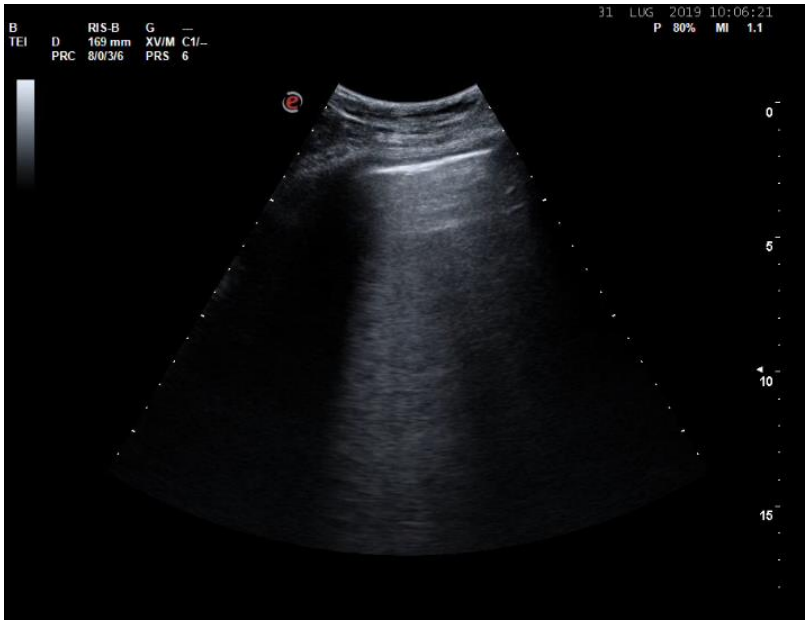


Figure 7. Pattern B: multiple B lines (> 3 for intercostal space) originating from the pleural line and reaching the bottom of the screen without fading, moving together with the pleural sliding.

The "interstitial syndrome" can therefore be defined as a condition determined by the presence of minimal quantities of fluid that is added to the physiological air component of the alveolar, whether it is cardiogenic or not (eg ARDS). The picture is characterized by the finding of an excessive number of B lines in different areas of the lung (Figure 8).

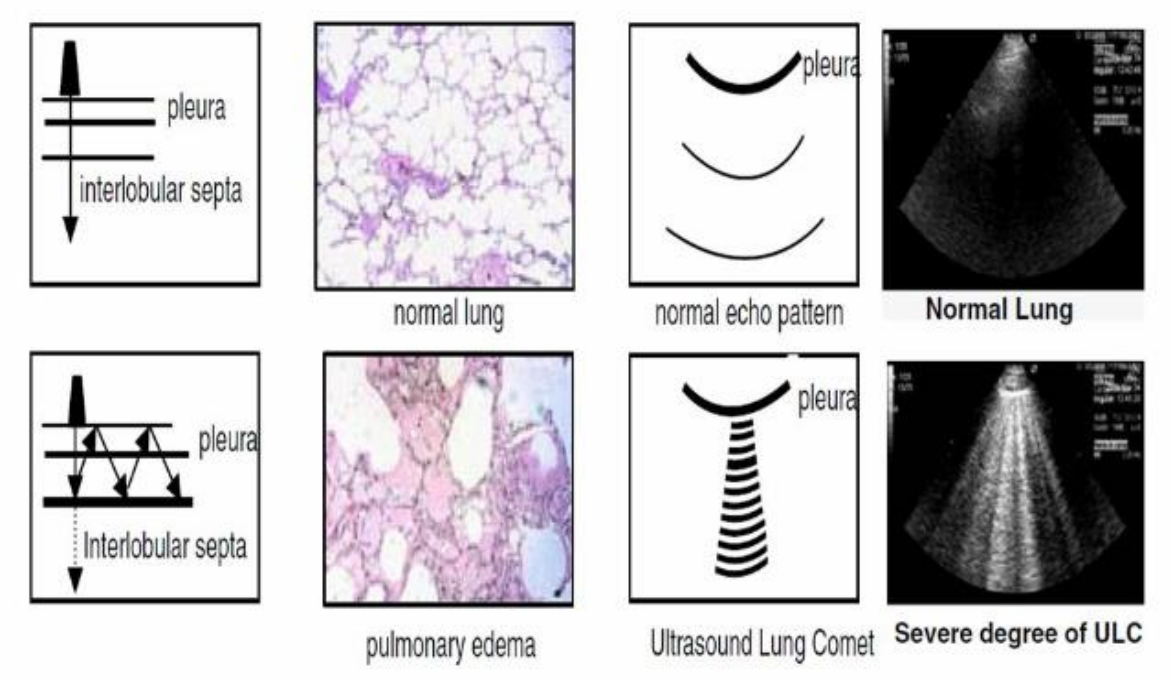


Figure 8. Genesis of the B lines(36)

For "lung rockets" (the wake of a departing rocket) or "B + scan" we mean a bundling of B lines in a single lung scan. (according to the 2012 Consensus it would be better to use the term " B-pattern " to describe this picture)(34) (Figure 9).

The presence of multiple “B pattern” scans in each lung, in different anterolateral or lateral scans, configures a picture of diffuse interstitial syndrome. More precisely, this syndrome is commonly defined by the presence of bilateral engagement, in at least two scan areas out of four per hemithorax(35).

As it is possible, as mentioned above, the presence of B lines in physiological conditions and since there is the possibility that close B lines are also present in the surrounding areas, parenchymal thickening of various origins (contusion, atelectasis, pneumonia, tumour)(37)(38), the detection of B lines in some areas of the chest is not necessarily correlated with a diffuse interstitial pathology.

It is therefore very important to recognize pattern B in multiple scans for each hemithorax in order to be able to diagnose diffuse interstitial syndrome (39).

The finding of B-line artefacts in the patient with interstitial disease is also often associated with other ultrasound changes, such as thickening (85%) or irregularity (98%) of the pleural line or the presence of subpleural formations (37%) (32).

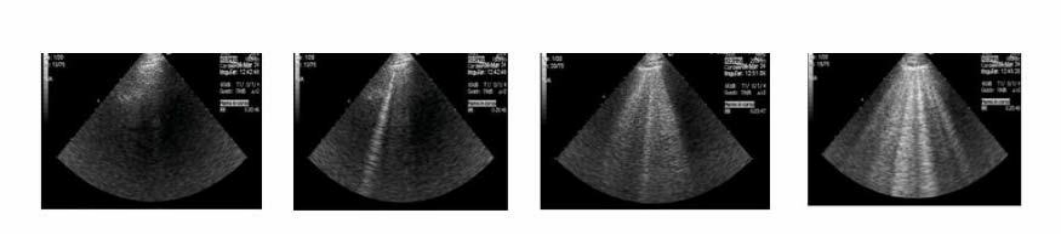


Figure 9: From left: normal lung picture (“black” lung); isolated B lines; “wet” or “black-white” lung; “white” lung, with interstitial syndrome. Adapted from Soldati, G et al (32)

It has been shown that the separation between the B lines should not exceed 7 mm (the distance that reflects that between 2 interlobular septa with sub-pleural localization)(32)(35).

The presence of closer artefacts, about 3 mm apart from each other, would correspond to the involvement of the intralobular interstitium visible as a ground glass pattern or as a micro crosslinking on high resolution CT.

From these assumptions it is clear that the ultrasound artefact being analysed reflects, though in a non-anatomically manner, the condition of the pulmonary interstitial.

The B lines are extremely dynamic, changing in real time in relation to changes in lung tissue density. They are therefore early and reliable indicators of interstitial involvement, even before radiographic alterations or worsening of oxygen exchanges are visible.

Pulmonary overload is evident on early ultrasound. In an experimental model of lung damage induced by oleic acid (an animal model that allows the detection of the earliest phase of respiratory distress syndrome / non-cardiogenic pulmonary oedema)(30)(32). it was observed that the reduction of the P / F less than 300 appears at least 90 minutes after injection, while B lines are already significantly increased at 15 minutes after injection and continue to increase linearly over time(36).

At least in the experimental setting, the ultrasound data therefore allows a diagnosis of lung damage even earlier than the blood gas analytical parameter and this pathophysiologically

could be explained by the fact that, in the initial phases, even the simple perilobular venous distension, which occurs during the phases of decompensation due to the increase in pulmonary venous pressure, modifies critically the relationships between air and liquid at the level of the subpleural interlobular septa and therefore genera, always through the mechanisms mentioned above, the B lines(32)

Many studies have highlighted the correlations between ultrasound and clinical imaging, and still others are experimenting with the use of quantitative methods for the definition of interstitial syndrome, or developing software for the automatic interpretation of ultrasound images (Figure 10).

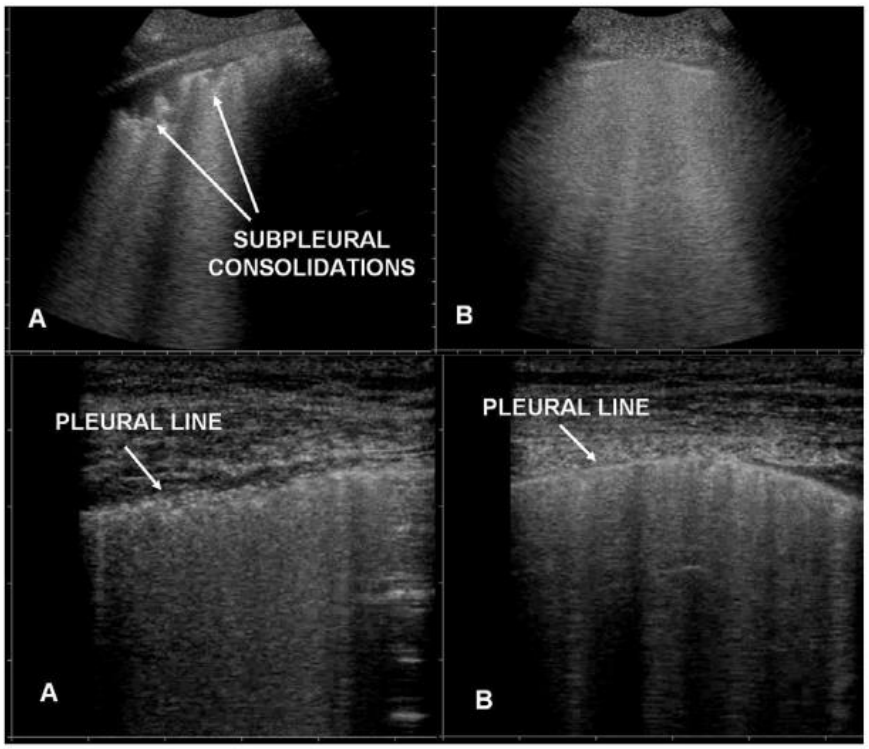


Figure 10: ARDS (A) and cardiogenic pulmonary oedema (B). Small subpleural consolidations present in ARDS (A, top), absent in cardiogenic pulmonary oedema (B, top). Altered pleural line in ARDS (A, below), normal in cardiogenic pulmonary oedema (B, below). From Copetti, R et al(30).

Objectives of the study

The Berlin definition, currently accepted for the diagnosis of ARDS, requires the execution of an x-ray or computed tomography (CT) of the chest, measurement of blood gases (arterial blood gas analysis), and the use of a positive ventilation pressure (40).

On the one hand, these diagnostic-therapeutic tools are not always easily available in contexts within limited resources hospitals, and on the other they require the use of radiation and invasive procedures in more developed contexts. Some studies also suggest that lung ultrasound may be superior to chest x-ray, relative to the reference standard CT, in determining the presence of bilateral opacities, and that arterial blood gases and minimal PEEP may not be necessary to get a diagnosis of ARDS(15).

The investigation conducted in Kigali, Rwanda, led to a modification of the Berlin definition, using pulse oximetry and pulmonary ultrasound to determine the incidence, clinical characteristics and outcome of ARDS in a referral hospital located in a low-income country. This study was the first to evaluate the incidence of ARDS within the entire hospital, and not only in the Intensive Care Unit. The most significant conclusions were that non-ventilated patients with clinical features of ARDS have a poor prognosis, and could therefore represent a high-risk population that could benefit from timely intervention, and that the modified definition of ARDS could be applied to patients of all hospital departments. The identification of patients who meet the 'Kigali modification' criteria for ARDS could allow faster recognition and more appropriate treatment, and facilitate multicentre epidemiological and interventional studies(18).

In the NITWA ARDS study ("I am ARDS") the hypothesis is that the hospital incidence of ARDS, defined according to the Kigali modification, may be similar in resource intensive settings (e.g. Toronto and Turin) compared to contexts with more limited resources such as Kigali, Rwanda. In addition, lung ultrasound could be a more sensitive and equally specific imaging method compared to chest radiography in identifying bilateral opacities, in relation to the CT reference standard.

The objectives of this prospective multicentre cohort study were therefore:

• **Objective 1**: Evaluate the hospital incidence of ARDS, both according to the Berlin definition and according to the Kigali modification.

- 1A: Describe the clinical population characteristics and outcomes of patients enrolled with hypoxemia, correlating the data collected (for example, degree of hypoxemia and respiratory rate with outcomes such as mortality, hospital stay times, increase in the intensity of care).

- 1B: Analysing the prognosis and temporal evolution of patients who initially meet the criteria for ARDS defined according to Kigali, and subsequently progress to ARDS defined according to Berlin.

-

• **Objective 2**: For the subgroup of patients who undergo chest CT scan, determine the sensitivity and specificity of chest radiography and ultrasound, performed within 12 hours, in identifying bilateral opacities, in relation to the CT reference standard.

A pilot study was also performed with the specific aim of estimating the feasibility of the multicentre part. The criteria used to assess feasibility included:

a. Number of inpatient adults who meet the criteria for ARDS according to Kigali or Berlin during the first 7 days of hospitalization;

b. Number of adult hospitalized patients with / developing hypoxemia, identified at daily screening, during the first 7 days of hospital admission (% hypoxemic patients / new admissions);

c. Proportion of patients recruited / eligible patients (see below for eligibility criteria);

d. Workload for each patient (time required for lung ultrasound scan; average time required for data collection during the first day of hypoxemia);

e. Proportion of patients with chest x-ray, CT, and ultrasound available within the same day +/- 1.

Methods

Study protocol and definitions

The feasibility phase of the study was performed at Toronto Western Hospital (TWH), Toronto, Canada and Beth Israel Deaconess Medical Center (BIDMC), Boston, USA. In this phase, the study protocol was evaluated within a TWH hospital ward (initially for 1 day and then for 7 days). After modifying the protocol on the basis of what was learned from the pre-pilot study, a pilot study was conducted involving all hospital wards of TWH and BIDMC (excluding Post-Operative Resuscitation, but including First Aid). After completing the feasibility phase, the actual, prospective, observational study of a multicentre cohort began (Figure 11).

Figure 11. Phases of the study

Study design

The study in Italy was conducted at two hospitals in Turin, the University Hospital "Città della Salute e della Scienza" and "San Giovanni Bosco" hospital. We performed a prospective observational cohort study, as part of a multicentre cohort study.

Study population and data collection

All adult patients (≥ 18 years old) admitted to hospital during the study period, both summer and winter, were screened/asked daily for the development of hypoxemia (defined as oxygen saturation <90%) or supplemental oxygen utilization, for a total of 5 days for screened patients and 7 days of follow up for each patient enrolled in those 5 days (Figure 17- Flow chart, placed at the part supplementary material below). Data regarding oxygenation and the use of supplemental oxygen were obtained through the review of medical records (including electronic data). The screening data was collected into a special form for screening log.

The consent was verbal, with the possibility of revoking and exiting the study at any time. All screening and enrolment data were collected in the REDCAP controlled access database.

We included all patients above 18 years old that were admitted to the hospital during the study period. As eligible for enrolment we considered patients either with new onset of hypoxemia (SoO2 < 90% or use of any supplemental oxygen) or, if patients that were already on home oxygen treatment, had the need to higher than baseline oxygen flow during the first 7 days of hospitalisation.

Patients that stayed in the Emergency Department, but were not formally admitted to the hospital and patients admitted in PACU or to Psychiatry ward were not taken into account and were excluded from our study.

Individual data collection for enrolled patients

For each eligible patient during the study period, we collected the data listed in the table below (Table 2), subject to obtaining informed consent.

Day 1 of hypoxemia detection	
Data extracted from patient's medical records	
Baseline demographic characteristics (age, gender, height, weight, race/ethnicity)	
Hospital Data (type of recovery – elective or urgent admission; transfer vs direct admission vs ED admission-; date of original admission; if transfer from other hospital; patient service at time of study measurements (different wards : medical, surgical, ICU)	
Main diagnosis/clinical presentation	
Co-morbidities (Deyo-Charlson Comorbidity Index)	
Risk factors for ARDS at admission in hospital	
New or worsening symptoms at the last 7 days	
Start of mechanical ventilation (invasive or non-invasive)	
Oxygenation data	
Oxygen saturation (SpO_2)	
Oxygen delivery device and flow rate and/or FIO_2	
PEEP , if mechanically ventilated	
Respiratory Rate	
Arterial blood gas (when available)	
SpO2/FiO2	
Imaging data	
Lung ultrasound	Focused lung ultrasound (12 areas of investigation)
Chest imaging	New chest imaging (CXR and/or CT) performed in the past 24 hours

Day 2-6 after hypoxemia detection	
Oxygenation data	Oxygen saturation (SpO_2)
	Oxygen delivery device and flow rate and/or FiO_2
	PEEP (if mechanically ventilated)
	Respiratory rate
Lung ultrasound data	Focused lung ultrasound (12 areas of investigation)
Chest imaging data	New chest imaging (CXR and/or CT) performed in the last 24 hours.

Day 7 after hypoxemia detection	
Aetiology	Aetiology of the hypoxemia (as written in medical records)
	Newly identified risk factors for ARDS
	Need for ICU recovery in the first 7 days
	Starting with mechanical ventilation (Invasive or non-invasive) during the first 7 days
Oxygenation data	Oxygen saturation (SpO2)
	Oxygen delivery device and flow rate and/or FiO_2
	PEEP (if mechanically ventilated)
	Respiratory rate
Lung ultrasound data	Focused lung ultrasound (12 areas of investigation)
Chest imaging data	New chest imaging (CXR and/or CT) performed in the last 24 hours.

Outcome data collection	
Data extracted from the medical record of the patient	Vita status at at hospital discharge, censored 90 days post-enrolment ICU admission during hospitalization Discharge disposition Institution of comfort measures or palliative care prior to death

Definitions

For the purposes of our study we used the Berlin definition and the Kigali modification.

The Berlin definition proposed by Ranieri et al contains the following elements in tat should be fulfilled in order to get to ARDS diagnosis:

- onset of ARDS within one week of a clinical insult
- $PaO2 / FiO2 \leq 300$ mmHg
- PEEP of at least 5 cmH2O
- Bilateral chest X-ray or CT opacities that are not fully justified by effusion, collapse or nodules, and opacities not fully justified by heart failure.

Instead of this the Kigali modification illustrated by Riviello et al contains the following parameters that need to be fulfilled [18]:

- $SpO2 / FiO2 \leq 315$ (with $SpO2 \leq 97\%$)
- PEEP not required
- bilateral chest X-ray or CT opacities not fully justified by effusion, collapse or nodules, and opacities not fully justified by heart failure.

The table (Table 3) below illustrates the elements of the Berlin definition and the Kigali modification.

		Berlin	Kigali
Timing		Within 1 week of a known clinical insult or new or worsening respiratory failure	
Oxygenation	PaO_2/FIO_2	≤ 300	×
	SpO_2/FIO_2	×	≤ 315 (with SpO_2≤ 97%)
Positive pressure		Mandatory (minimum PEEP 5 cm H_2O)	No PEEP requirement
Imaging*	*CXR*	✓	✓
	LUS	×	✓
	CT	✓	×
Origin of edema		Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment to exclude hydrostatic edema if no risk factor present)	

* bilateral opacities not fully explained by effusion, collapse or nodules, and opacities not fully explained by cardiac failure

Table 3. Definitions used for the study.

Lung ultrasound definitions in the study

Artifacts identified by placing the probe on ventilated lung tissue can be:

normal, abnormal but without pathological significance or related to pathological entities.

- **A-Lines**: horizontal hyperechoic lines with increasing depth separated by the same distance existing between the probe and the pleural line. Consider reverberation artifacts originating from strong reflectivity between the probe and pleural line interfaces.

- **B-Lines**: discrete laser-shaped, vertical, hyperechoic artifacts originating from the pleural line, extend to the bottom of the screen without fading, and move synchronously with pleural sliding.

- **"Pattern A":** presence of A lines, alone or associated with less than 3 B lines

- **"Pattern B":** presence of three or more B lines / intercostal space (sagittal scan), which represent a region of increased lung density [2]. Moderate pulmonary ventilation loss (pattern B1): presence of ≥ 3 well-defined B-lines / intercostal space; Severe lung ventilation loss (pattern B2): multiple coalescing B-lines / intercostal space.

- "**Pattern C":** Lung consolidation ("pattern C"): Anechoic or tissue-like image (hepatization) originating from the pleural line which is limited in depth by an irregular border ('shred sign'). It represents an area of severely increased lung density with (almost) complete loss of ventilation.

- **Pleural effusion** - Anechoic (fluid) collection located between the parietal and visceral pleura, associated with positive spinal sign and absent tent sign.

For the purposes of defining ARDS by lung ultrasound, three different bilateral opacity definitions were used.

- Ultrasound finding of pattern B (B1 or B2) or consolidation (pattern C) in at least one area on each hemithorax (definition of Kigali - 2 areas);

- Ultrasound finding of pattern B (B1 or B2) or consolidation (pattern C) in at least two areas on each hemithorax (Kigali definition - 4 areas);

- Ultrasound findings of 1) pattern B2 or C in at least two areas on each hemithorax, or 2) pattern B1 in at least three areas on each hemithorax, or 3) pattern B2 or C in at least one area and pattern B1 in at least two areas on each hemithorax, or 4) pattern B2 or C in at least two areas on one hemithorax and pattern B1 in at least three areas (or pattern B2 or C in at least one area and pattern B1 in at least two areas) on the other hemithorax (definition of Kigali - more restrictive criteria).

A moderate / severe effusion (defined as volume of pleural fluid> 500) could cause atelectasis and therefore not represent opacities directly related to ARDS. To determine the effect of pleural effusion volume on the correct identification of ARDS-related opacities, separate analyzes were performed considering ARDS-related consolidations 1) only those identified in patients with mild pleural effusion and 2) all bilateral consolidations regardless of the volume of associated pleural effusion (ie, including mild, moderate and severe effusions).

To estimate the size of the effusion on pulmonary ultrasound, the formula described by Usta et al (41) was used. After identifying the pulmonary base and the pleural effusion at the end of expiration, the maximum distance between the median height of the diaphragm (point A) and the visceral pleura on the consolidated lung (point B) was measured. This distance (D) was related to the pleural effusion volume by the formula: Vpe (mL) = 16 x D (mm). Therefore, a distance D of less than 30 mm correlates with a pleural effusion volume of less than 500 mL (mild effusion).

Bilateral opacities

Chest X-ray is marked positive for bilateral opacities when opacities are recognized in at least two quadrants, one on each side of the chest, interpreted as not justified solely by effusion, collapse, or nodules. The CT exam is interpreted in the same way. Chest x-rays and CT scans will be read by an experienced physician at each site, with 10% independent review by a second physician.

Pulmonary Ultrasound - Methods of Execution in the Study

1. All patients were examined in a semi-sitting position when possible.

2. An ultrasound system with a low frequency curvilinear-array transducer at 5-1 MHz was used. The system was set up according to the pulmonary ultrasound protocol (removal of the second harmonic and any subsequent automatic processing, to avoid the attenuation of artifacts).

3. All intercostal spaces of the upper and lower areas of the anterior, lateral and posterior regions of the right and left sides of the chest wall (12 survey areas) were examined by sagittal scan. The anterior thorax was identified in the space between the parasternal line and the anterior axillary line; the lateral thorax in the space between the anterior axillary line and the posterior axillary line; the posterior thorax in the space between the posterior axillary line and the spine (excluding the scapular area) (Figure 12).

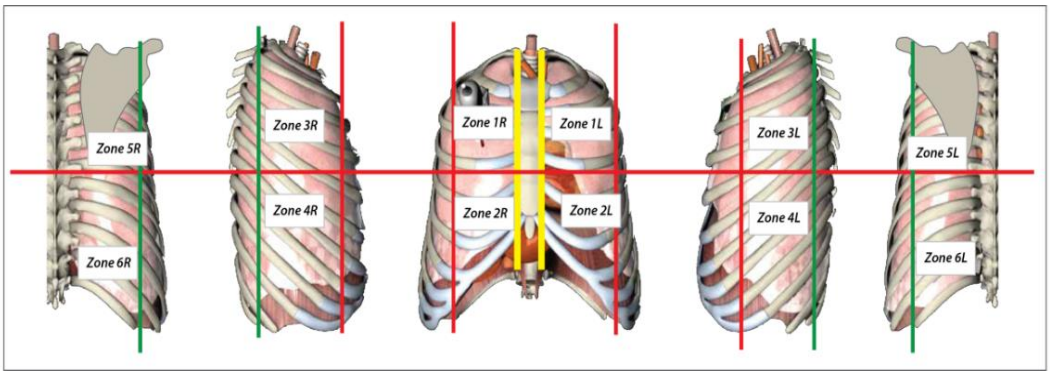


Figure 12. Schematic diagram of the 12 investigation areas of the thoracic ultrasound

4. The ultrasound settings were as follows: the focus was set at the level of the pleural line, the gain was adjusted to maximize the contrast between the pleural line and intercostal muscles. A standard depth of 10 cm below the pleural line was used to allow standardization.

5. The worst ultrasound abnormality identified was considered to characterize the region under examination.

6. For the lung bases, the probe was positioned approximately at the level of the 9th-11th intercostal space on the right and left middle axillary line, with the ultrasound beam slightly posteriorized (towards the more dependent areas of the pleural cavity - taking care of identify the patient's spine). The depth was set at 12-20cm.

7. The 6-second ultrasound films were saved on a hard drive in AVI format (acceptable format, preferably DICOM in other centers). An attempt was made to keep the probe as still as possible and perpendicular to the pleural line to facilitate post-acquisition analysis.

Demographical characteristics, clinical and outcome variables are presented as number or percentage for categorical variables, while for continuous variables we used means with standard deviations or medians with interquartile ranges (IQRs)

Incidence will be calculated as the proportion of patients admitted during the one-week study period who develop Berlin or Kigali ARDS during the one-week study period or one week of additional follow up. We performed univariate analyses to in order to access and determine the association between various variables of interest.

Statistical analyses were conducted using STATA software, version 13.1 (Stata Corporation, College Station, Texas, USA).

Results

The study was conducted during the summer season (in July 2019) and during the winter season (in February 2020) at two hospital centres in the city of Turin, Italy: The A.O.U. Citta delle Scienze e della Salute - former Molinette Hospital, where the screening period took place from 1/7/2019 to 5/7/2019 and from 2/2/2020 to 6/2/2020, and the San Giovanni Bosco (S.G.Bosco)

Hospital, where the screening period took place from 29/7/2019 to 2/8/2019 and from 20/01/2020 to 24/01/2020.

As defined in the study protocol, each patient included in the screening was followed for 7 days, evaluating the possible development of hypoxemia every day. If a patient became hypoxemic during the 7 days of screening, he/she was enrolled in our study and underwent an assessment of the parameters related to respiratory function and chest ultrasound for a further time of 7days.

Demographic characteristics:

At the Molinette hospital, 559 patients were screened (235 females, 324 males), of which 97 enrolled (43 females, 54 males; age = 71.00 ± 14.01, range 33-92; median 74) during the two one-week study periods (summer and winter). At the S.G.Bosco hospital, 313 patients were screened (132 females, 181 males), of which 49 enrolled (20 females, 29 males age = 71.27 ± 13.22, range 29-96; median 74).

The total number of 872 patients with hypoxia were screened and 146 enrolled patients. All enrolled patients were Caucasian.

In total 35% of the patients screened in the hospital S.G.Bosco, (111; 65 in summer, 46 in winter) underwent elective hospitalization, while 65% (202; 95 in summer, 107 in winter) underwent an emergency hospitalization. For the Molinette hospital, we observed 43% of elective hospitalizations (243; 97 in summer, 146 in winter) and 57% of emergency hospitalizations (316; 156 in summer, 160 in winter). There is a general trend for a greater proportion of emergency hospitalizations in the winter season (log odds ratio = .46, z = .46, p = .052), in particular for the hospital centre San Giovanni Bosco (log odds ratio = -.84, z = .85, p = .004).

For patients of the hospital centre S.G.Bosco, 57% (178) of medical hospitalizations (85 in summer, 93 in winter) and 43% (135) of surgical hospitalizations (75 in summer, 60 in winter) were observed. For the Molinette hospital, we detected 65% of medical hospitalizations (365; 169 in summer, 196 in winter) and 35% of surgical hospitalizations (194; 84 in summer, 110 in winter). There is no significant seasonal difference between the two types of hospitalization (log odds ratio = -.31, z = .31, p = .172), but there is a higher proportion of surgical admissions to the S.G.Bosco (-.57 = .10, z = .57, p = .006).

Overall, 26 patients received home oxygen therapy (7 patients from the S.G.Bosco, 19 patients from Molinette hospital).

When we went into details at the comorbidities of the patients, taking into account the pathologies reported in the Deyo-Charlson Comorbidity Index (as proposed by protocol), the most frequently observed comorbidity (~ 6% of cases) was chronic lung infection, followed by malignant tumours (~ 5% of patients) (Figure 13, 14, 15, 16).

Weight	Clinical condition
1	Myocardial infarct Congestive cardiac insufficiency Peripheral vascular disease Dementia Cerebrovascular disease Chronic pulmonary disease Conjunctive tissue disease Slight diabetes, without complications Ulcers Chronic diseases of the liver or cirrhosis
2	Hemiplegia Moderate or severe kidney disease Diabetes with complications Tumors Leukemia Lymphoma
3	Moderate or severe liver disease
6	Malignant tumor, metastasis Aids

Figure 13. Deyo-Charlson Comorbidity Index

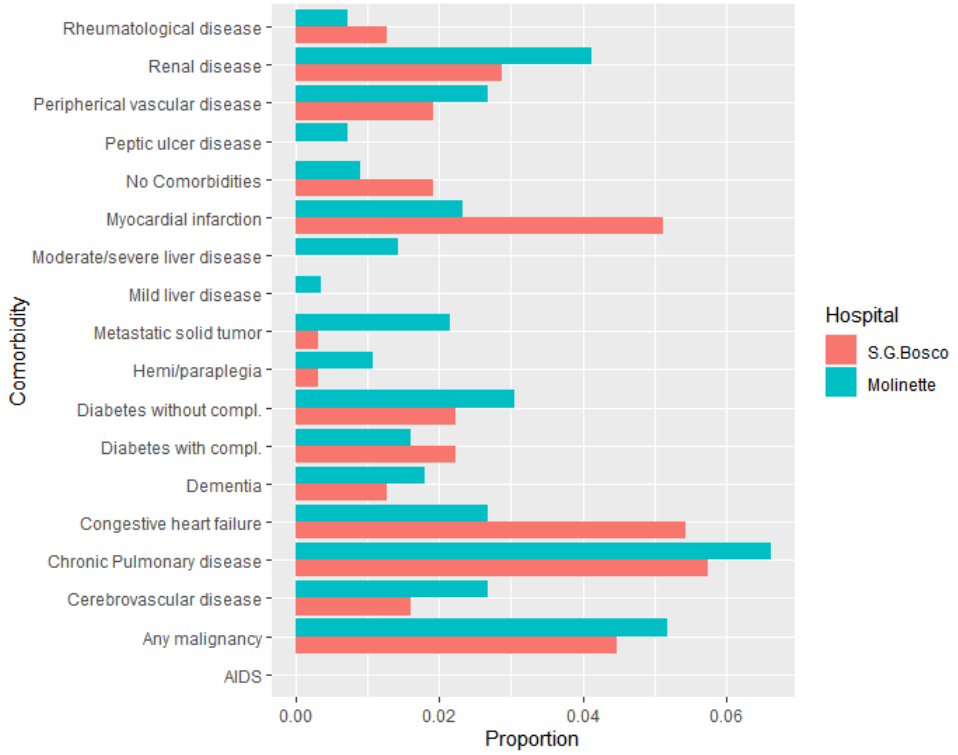


Figure 14. Proportion of patients with comorbidities at the two hospitals.

At the level of seasonal variation, we observed that the S.G.Bosco experienced more comorbidities during the winter season, particularly for cardiac pathologies. This phenomenon is in accordance with the fact, already noted, that the S.G. Bosco made significantly more emergency hospitalizations in the winter.

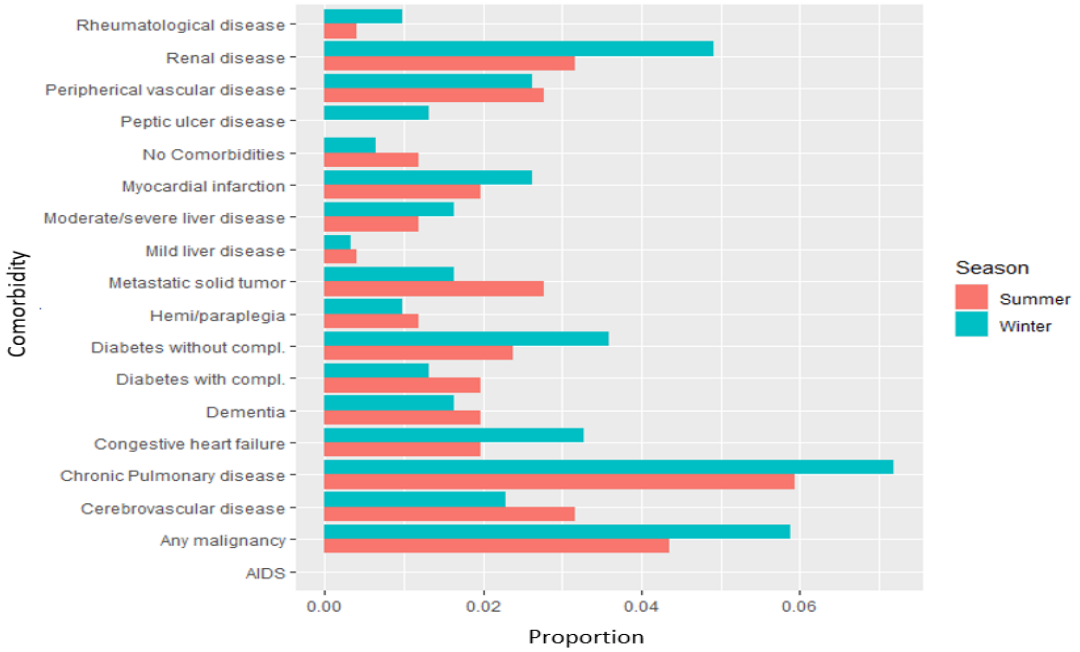


Figure 15. Seasonal variation in comorbidities for Molnette hospital.

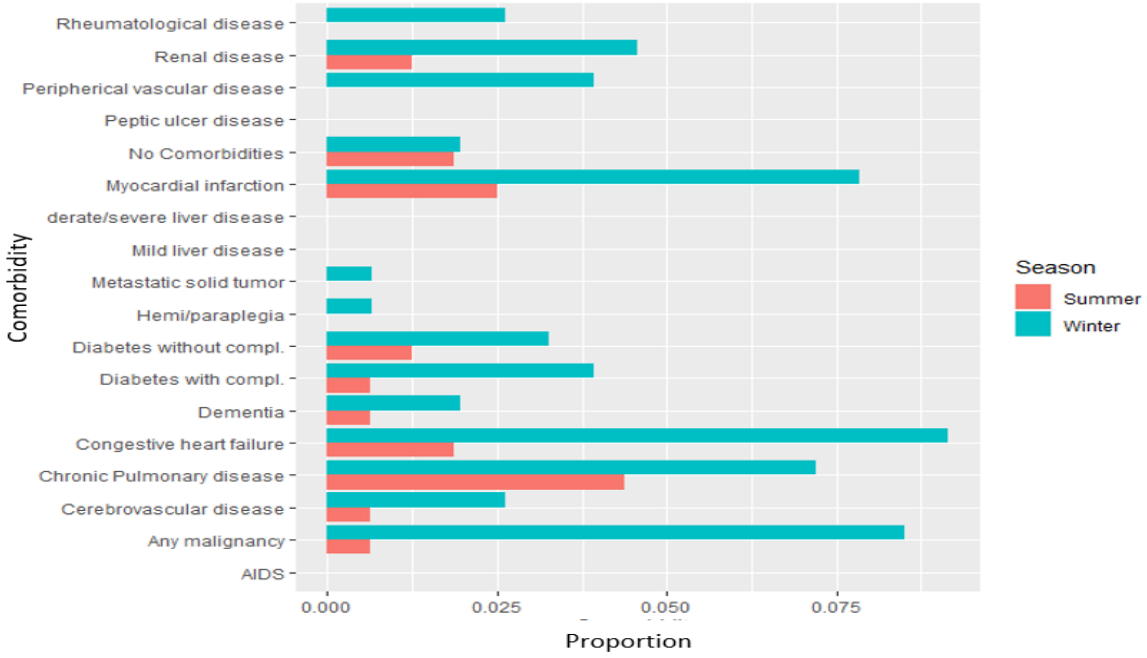


Figure 16. Seasonal variation in comorbidities for S.G. Bosco.

At the end of hospitalization for both hospitals, at hospital discharge (following the criteria of the ICD-9-CM manual), 83 patients (57%) received a diagnosis of respiratory disease, of which 4 enrolled patients were discharged with a principal diagnosis of ARDS (3%).

A discharge diagnosis of respiratory disease was present in 49% (48) of the patients of Molinette hospital and 71% (35) of the patients from S.G. Bosco. The difference in incidence is statistically significant (log odds ratio = .394, p = .013).

Table 4. Frequency of the types of diagnosis on patients admitted to the two hospital centres.

Diagnosis	All patients	Number of patients at Molinette	Number of patients at . S.G.Bosco
Respiratory Disease	83 (57%)	48 (49%)	35 (71%)
We observed Cardiovascular Disease	61 (42%)	39 (40%)	22 (45%)
Metabolic/Renal/Endocrine/Autoimmune Disease	23 (16%)	18 (19%)	5 (10%)
Neurologic Disease	16 (11%)	14 (14%)	2 (4%)
Shock	16 (11%)	13 (13%)	3 (6%)
Gastrointestinal/Hepatic Disease	15 (10%)	13 (13%)	2 (4%)
Other (Non-operative)	13 (9%)	11 (11%)	2 (4%)
Gastrointestinal, hepatobiliary and pancreatic surgery	11 (8%)	9 (9%)	2 (4%)
Mental or Behavioural Disorder	8 (5%)	6 (6%)	2 (4%)
Hematologic Disease	7 (5%)	7 (5%)	0 (0%)
Cardiac / aortic surgery	4 (3%)	4 (4%)	0 (0%)
Urologic surgery	3 (2%)	2 (2%)	1 (2%)
Trauma	3 (2%)	1 (1%)	2 (4%)
Neurosurgery	2 (1%)	2 (2%)	0 (0%)
Thoracic surgery	2 (1%)	0 (0%)	2 (4%)
Bariatric surgery	1 (1%)	1 (1%)	0 (0%)
Transplant	1 (1%)	1 (1%)	0 (0%)
Vascular surgery (non aortic)	1 (1%)	1 (1%)	0 (0%)

Focusing only on patients with diagnosis of respiratory diseases, we observed 35 patients with diagnoses of COPD (24% of total hospitalizations), 32 patients with viral / bacterial pneumonia (22%), 8 patients with neoplasms (5%), 4 patients with ARDS (3%), 2 patients with pulmonary embolism (1%), 2 patients with asthma / allergic reactions (1%), 2 patients with aspiration pneumonia (1%), 1 patient with mechanical airway obstruction (1%), and 28 patients were classified in the category "other" (19%). A total of 32 patients with heart failure (22%) were also observed, of whom 15 patients at Molinette hospital (15% of patients admitted to the centre) and 17 patients at S.G.Bosco hospital (37%).

In particular, dividing by the different centres, the percentages for the Molinette Hospital are: COPD 19 (20%), Pneumonia 17 (18%), Neoplasms 6 (6%), emboli 2 (2%), ARDS 1 (1 %), asthma / allergic reactions 1 (1%), aspiration pneumonia 1, Other 25 (26%)

For S.G.Bosco Hospital the percentages are: COPD 16 (34%), Pneumonia 15 (32%), ARDS 3 (6%), Neoplasms 2 (4%), asthma 1 (2%), mechanical obstructions 1 (2%), aspiration pneumonia (2%), Other 3 (5%). The data distribution in regards to the final diagnoses divided by season is shown in Table 5.

Table 5. Frequency of the types of diagnosis on hospitalized patients for the two hospital centres by season. The percentages refer to the total number of patients admitted to the centre during the reference season.

Diagnosis	Summer (H.C. Molinette)	Winter (H.C. Molinette)	Summer (H.C. Bosco)	Winter (H.C. Bosco)
Respiratory Disease	17 (40%)	31 (56%)	9 (75%)	26 (70%)
Cardiovascular Disease	16 (38%)	23 (42%)	8 (67%)	14 (38%)
Metabolic/Renal/Endocrine /Autoimmune Disease	9 (21%)	9 (16%)	2 (17%)	3 (8%)
Neurologic Disease	6 (14%)	8 (15%)	0 (0%)	2 (5%)
Shock	11 (26%)	2 (4%)	1 (8%)	2 (5%)
Gastrointestinal/Hepatic Disease	4 (10%)	9 (16%)	1 (8%)	1 (2%)
Other (Non-operative)	4 (10%)	7 (13%)	2 (17%)	0 (0%)
Gastrointestinal, hepatobiliary and pancreatic surgery	4 (10%)	5 (9%)	0 (0%)	2 (5%)
Mental or Behavioural Disorder	6 (14%)	0 (0%)	1 (8%)	1 (2%)
Hematologic Disease	2 (5%)	5 (10%)	0 (0%)	0 (0%)
Cardiac / aortic surgery	2 (5%)	2 (4%)	0 (0%)	0 (0%)
Urologic surgery	0 (0%)	2 (4%)	0 (0%)	1 (3%)
Trauma	1 (2%)	0 (0%)	2 (17%)	0 (0%)
Neurosurgery	2 (5%)	0 (0%)	0 (0%)	0 (0%)
Thoracic surgery	0 (0%)	0 (0%)	0 (0%)	2 (5%)
Bariatric surgery	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Transplant	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Vascular surgery (non aortic)	0 (0%)	1 (2%)	0 (0%)	0 (0%)

Clinical data analysis:

The trend of hypoxemia during the days, expressed as SpO2 / FIO2 ratio, does not show statistically significant differences over the days of hospitalization (Figures 22-23; b = 2.29, t (317) = .37, p = .715). The SpO2 / FIO2 ratio does not show statistically significant differences either by hospitalization centre (b = -6.11, t (317) = -.21, p = .831), or by season (b = -10.98, t (317) = -.40, p = .687).

However, a greater lack of homogeneity in the data relating to the winter period is appreciated at the Giovanni Bosco hospital, with a trend towards lower SpO2 / Fio2 values compared to the summer period, in the days following the first.

Data on the association between mortality and hypoxemia are shown in Table 6. Higher mortality is found for patients with SpO2 / FiO2 ratio <235 (log odds ratio = 2.28, z = 3.60, p <.001) and for patients with SpO2 / FiO2 ratio between 235 and 315 (log odds ratio = 1.15, z = 2.05, p=.041), with no difference by centre or season.

Table 6. Mortality stratified by degree of hypoxemia. The percentages refer to the total of patients with that average degree of hypoxemia in the centre and in the season reported below in the table.

SpO2/FiO2 ratio	Total number of death cases	Mortality Molinette (Summer)	Mortality Molinette (Winter)	Mortality S.G.Bosco (Summer)	Mortality S.G.Bosco (Winter)
> 315	5 (9%)	3 (14%)	0 (0%)	1 (75%)	1 (13%)
≥235 ≤315	16 (24%)	3 (21%)	8 (29%)	1 (20%)	3 (15%)
<235	12 (48%)	3 (50%)	4 (50%)	1 (100%)	4 (44%)

Data on length of stay for surviving patients based on degree of hypoxemia are shown in Table 7. Length of stay is statistically significantly longer for patients with SpO2 / FiO2 ratio <235 (b = 18.49, t (102) = 3.66, p <.001), but there are no differences between the centres considered.

Table 7. Length of stay (LOS in days) stratified by degree of hypoxemia.

SpO2/FiO2 ratio	Length of stay (days)	LOS Molinette (Summer)	LOS Molinette (Winter)	LOS S.G.Bosco (Summer)	LOS S.G.Bosco (Winter)
> 315	14.79 ± 13.73	11.16 ± 9.21	18.42 ± 16.09	9.00 ± 6.93	17.29 ± 17.97
≥235 ≤315	15.10 ± 10.89	12.74 ± 6.50	22.18 ± 16.50	11.00 ± 13.89	12.88 ± 8.49
< 235	30.73 ± 29.35	45 ± 45.22	40	16	21.40 ± 13.74

Data on the association between ICU access and hypoxemia are shown in Table 8. Greater accesses are found for patients with SpO2 / FiO2 ratio <235 (log odds ratio = 2.67, z = 4.32, p <.001) and for patients with SpO2 / FiO2 ratio between 235 and 315 (log odds ratio = 1.06, z = 2.04, p = .042), with no differences by centre or season.

Table 8. Access to intensive care by degree of hypoxemia. The percentages refer to the total of patients with that average degree of hypoxemia in the centre and in the season reported in the header.

SpO2/FiO2 ratio	Total number of ICU access	Number of ICU access Molinette (Summer)	Number of ICU access Molinette (Winter)	Number of ICU access S.G.Bosco (Summer)	Number of ICU access Bosco (Winter)
> 315	6 (11%)	1 (5%)	2 (11%)	2 (50%)	1 (13%)
≥235 ≤315	19 (28%)	4 (29%)	8 (29%)	2 (33%)	5 (25%)
< 235	16 (64%)	3 (50%)	7 (88%)	1 (50%)	5 (56%)

The difference between deceased and non-deceased patients in the mean SpO2 / FiO2 ratio over seven days is statistically significant: deceased patients have a mean ratio of 229.54, non-deceased patients 258.95 (t (37.13) = 2.63, p = .012).

The difference in the SpO2 / FiO2 ratio (mean over seven days) between ICU and non-ICU patients is statistically significant (mean of 232.41 for hospitalized, 260.76 for non-hospitalized; t (64.79) = 3.07, p = .003).

If we calculate the SpO2 / FiO2 ratio only for the first five days of hospitalization instead of the first seven, we observe that the difference between deceased and undead patients is significant (mean of 228.51 for deceased patients, 257.19 for undead patients; t (37.62) = 2.50, p = .017). The difference between ICU and non-ICU hospitalized patients is significant (mean of 230.57 for hospitalized, 259.41 for non-hospitalized; t (66.25) = 3.06, p = .003).

In Table 9 we showed the average respiratory rate of patients by centre and mortality (deceased vs not deceased). The association between respiratory rate and mortality is statistically significant (b = -.91, t (140) = -2.13, p = .035; lower respiratory rate for survivors). Although the observed difference is very small, so too is the variability of respiratory rate values found in general, thus leading to the aforementioned significance.

Table 9. Association between mean respiratory rate and mortality, divided by hospitalization centre and season.

Mortality	Mean respiratory frequency (both centres)	Mean respiratory frequency Molinette (Summer)	Mean respitatory frequency Molinette (Winter)	Mean respiratory frequency S.G.Bosco (Summer)	Mean respiratory frequency S.G.Bosco (Winter)
Dead	22.19 ± 1.73	21.77 ± 1.22	21.67 ± 2.28	20.81 ± .76	22.87 ± 1.92
Alive	21.92 ± 1.54	22.19 ± 1.62	22.65 ± 2.63	21.61 ± .69	22.18 ± 1.98

In Table 10 we showed the average respiratory rate of patients based on the centre and access to intensive care. The association between respiratory rate and ICU access is not statistically significant (b = -.72, t (141) = -1.78, p = .078), probably also for the smaller number of patients on whom to do the above analysis.

Table 10. Association between average respiratory rate and access to intensive care, divided by hospitalization centre and season.

ICU access	Mean respiratory frequency (both centres)	Mean respiratory frequency Molinette (Summer)	Mean respiratory frequency Molinette (Winter)	Mean respiratory frequency S.G.Bosco (Summer)	Mean respiratory frequency S.G.Bosco (Winter)
Yes	21.53 ± 1.84	20.73 ± 1.09	22.08 ± 2.42	21.22 ± .77	22.26 ± 1.09
No	22.14 ± 1.46	22.13 ± 1.61	20.58 ± 2.09	21.42 ± .89	22.35 ± 2.12

Ultrasound data analysis:

A total number of 92 patients out of 146 hospitalized patients (63%) were scanned with lung ultrasound for seven consecutive days of hospitalization (61 out of 97 patients for Molinette hospital; 31 out of 49 patients for the S.G. Bosco, 63% in the two hospitals). A number of 15 patients (10%) were discharged or died before the end of the seven days of observation, while 39 patients (27%), despite being hospitalized during the 7 days of enrolment, did not always have a daily ultrasound scan, or had at least one missing ultrasound scan over 7 days. The most frequent reason for not having the ultrasound scan is patient refusal (25 cases), followed by patient unavailability (3 cases), objections from the patient's family (2 cases), or other reasons (9 cases).

The available data regarding the individual ultrasound projections are instead to be reported not to the total of 146 patients, but to only 91 patients, since the single scans, acquired at the Molinette Hospital in the winter season, are still being reported.

Overall out of 91 patients, only 21 patients (23%) had all 12 ultrasound screenings for all measurement days. Of these, 20 were hospitalized at Molinette hospital (48% of the summer hospitalizations in the centre), and 1 was hospitalized during the summer period in the S.G. Bosco. Three adverse events were recorded for the patient during the ultrasound, and all of these patients were hospitalized in the winter period at the S.G. Bosco, but with no apparent causal link with the latter.

At least one image of effusion (either mild or moderate to severe) was observed in 63 hospitalized patients (69%), of whom 29hospitalized at. Molinette Hospital (69% summer hospitalizations) and 34 hospitalized at the C.O. Bosco (69% of hospitalized at the O.C. Bosco; 29 in winter, 78% of winter hospitalized, and 7 in summer, 42% of summer hospitalized). The presence of pleural effusion tends to show aspects of seasonality, as at the C.O. Bosco (the only centre for which there are winter data) more pleural effusions were observed in winter (log odds ratio = 1.62, z = 2.29, p = .022).

At least one consolidation image was observed in 71 hospitalized patients (78%), of whom 29 at the O.C. Molinette (83% of the C.O.'s summer hospitalizations) and 36 at the C.O. Bosco (73% of hospitalized at the O.C. Bosco; 28 in winter, 76% of winter hospitalized, and 8 in summer, 67% of summer hospitalized). The presence of densification images is not associated with the season (log odds ratio = .44, z = .61, p = .541).

The association between thickening images and effusions is high: 62 patients (68% of 91) with both, 19 patients with neither effusion nor thickening image, 9 patients with no effusion detected, but with thickening image, only 1 patient with effusion detected, but without thickening image (tetrachoric correlation: .95).

Considering only patients with pleural effusion (63), 11 (17%) died without access to intensive care, 4 (6%) were hospitalized in ICU and died, 36 (57%) survived without hospitalization in ICU, and 12 (19%) survived with ICU hospitalization. Access to IT and mortality are not associated to a statistically significant extent (X2 (1) <.001, p = 1).

Considering, however, only patients without pleural effusion (83), 10 (12%) died without access to intensive care, 8 (10%) were hospitalized in ICU and died, 48 (58%) survived without

hospitalization in ICU, and 17 (20%) survived with ICU hospitalization. Access to IT and mortality are not associated to a statistically significant extent (X2 (1) = 1.46, p = .228).

Clinical-ultrasound criteria analysis (Berlin and Kigali criteria)

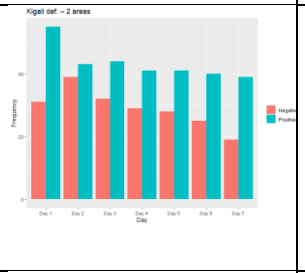
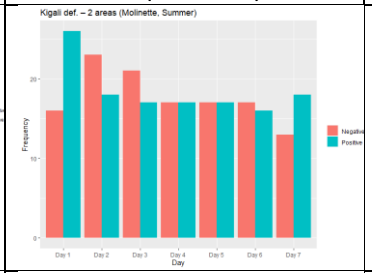
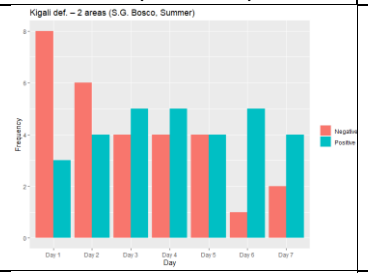
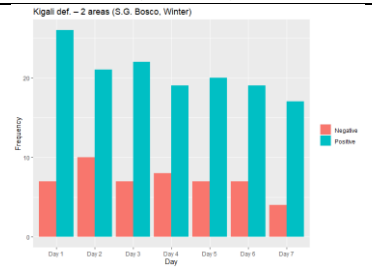
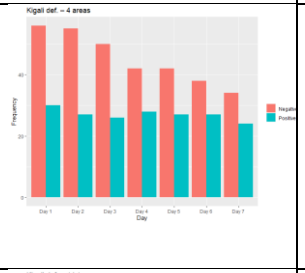
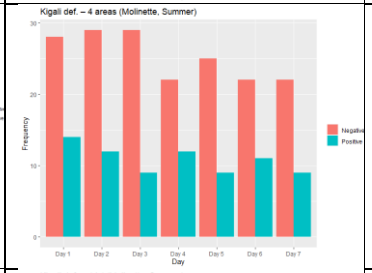
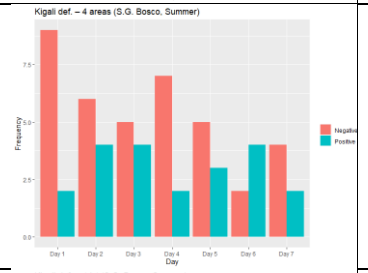
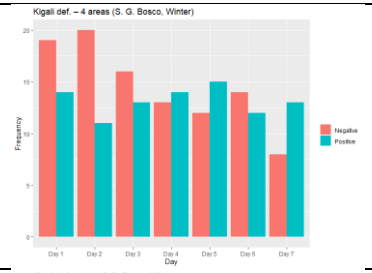
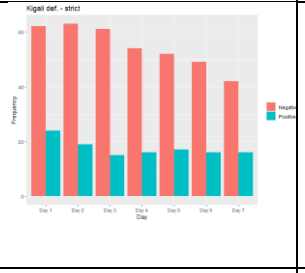
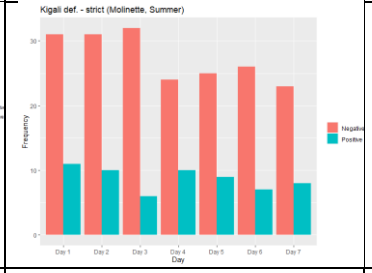
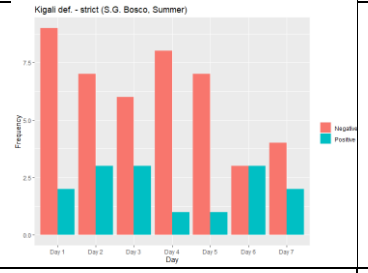
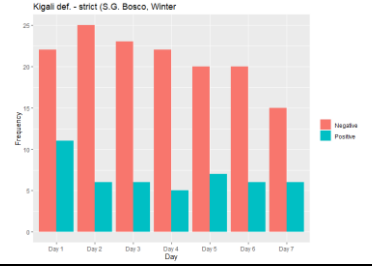
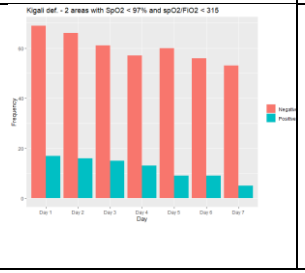
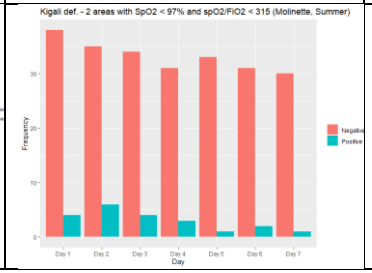
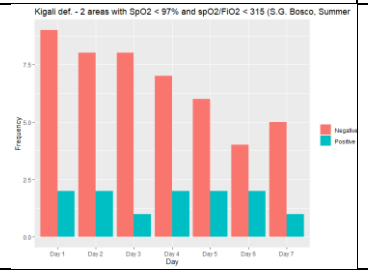
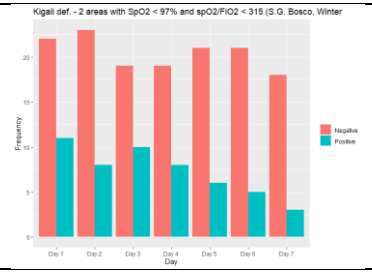
The data on the number of hospitalized patients who have reached (in at least one measurement) the Kigali intended only for 2-area, 4-area, and "strict" ultrasound and the Kigali intended as complete clinical and ultrasound criteria are shown in table 11, showed by centre and season.

Table 11. Patients with 2-area, 4-area, and strict Kigali in at least one measurement, divided by centre and season. The percentages refer to the total number of hospitalized at that centre in the indicated season.

Measure	Total number	Molinette (Summer)	S.G.Bosco (Summer)	S.G.Bosco (Winter)
Kigali 2 area	69 (75%)	32 (76%)	6 (50%)	31 (84%)
Kigali 4 area	57 (63%)	25 (60%)	5 (42%)	27 (73%)
Kigali strict	42 (46%)	20 (48%)	4 (33%)	18 (49%)
Kigali 2 area + SpO2/FIO2 <315 and SpO2 <97%	31 (34%)	11 (26%)	3 (25%)	17 (46%)
Kigali 4 aree + SpO2/FIO2 <315 and SpO2 <97%	26 (29%)	10 (24%)	3 (25%)	13 (35%)
Kigali strict + SpO2/FIO2 <315 and SpO2 <97%	20 (22%)	9 (21%)	3 (25%)	8 (22%)
Positive only to SpO2/FIO2	38 (42%)	11 (26%)*	7 (58%)	20 (54%)

The daily trend of patients with 2-area, 4-area and strict Kigali, divided by centre and season of admission, is shown in Table 12.

* With regard to the Molinette winter data, of which only an analysis of the clinical criteria of Kigali could be carried out, the latter 26 patients (47%) were reported positive since the total on all centres would be 64 patients (44%).

Measure	Total number	Molinette (Summer)	S.G.Bosco (Summer)	S.G.Bosco (Winter)
Kigali 2 areas				
Kigali 4 areas				
Kigali strict				
Kigali 2 areas + SpO2/FIO2 <315 e SpO2 <97%				

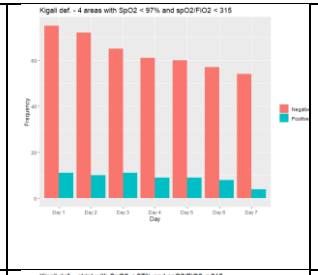
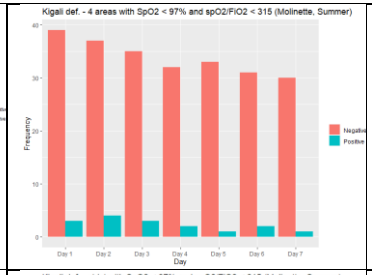
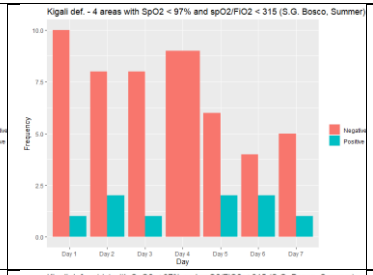
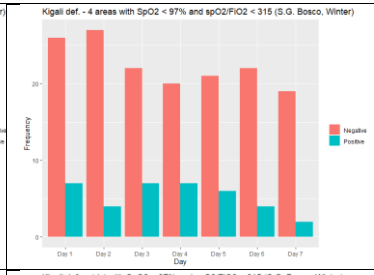
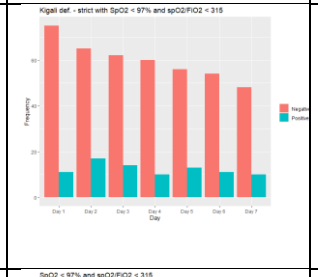
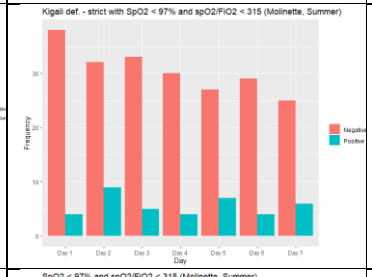
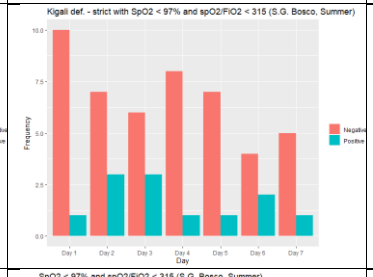
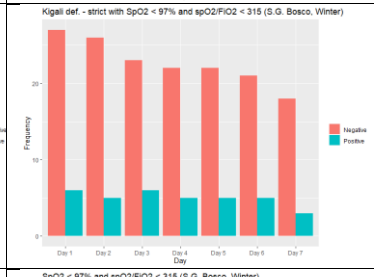
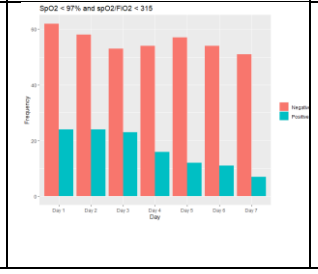
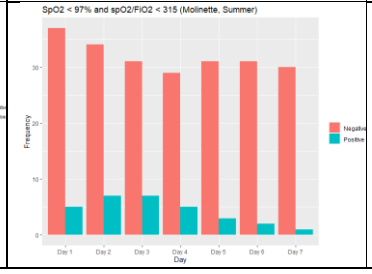
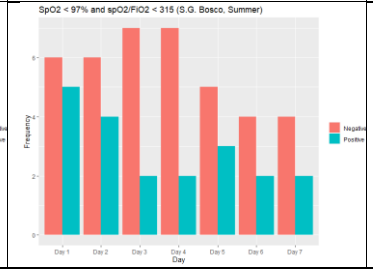
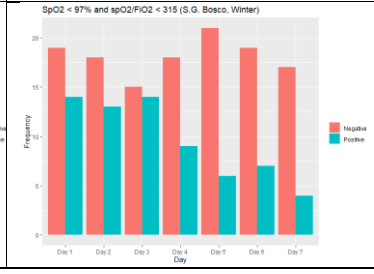
Kigali 4 areas + SpO2/FIO2 <315 e SpO2 <97%				
Kigali strict + SpO2/FIO2 <315 e SpO2 <97%				
Positive only to a SpO2/FIO2				

Table 12. Daily trend in the number of patients hospitalized with Kigali in 2 areas, 4 areas, and 'strict' by hospitalization centre and region. In blue the patients positive to the criterion.

There appears to be a slight tendency towards greater positivity in the first few days of hospitalization, especially for some centres in two-area Kigali.

As regards the Berlin criteria, 16 positive patients are observed (11% of the total), also counting the data from winter at Molinette hospital, despite the final diagnosis of ARDS in discharge was given only in 3% of cases. total (of these 16, 11 hospitalized at Molinette in winter, 69%, 4 hospitalized at Molinette in summer, 25%, and 1 hospitalized at S.G. Bosco in winter, 6%).

Considering only the patients positive to the Berlin criterion (16), it is observed that 6 (37%) died after admission to intensive care, 9 (56%) were hospitalized in ICU and survived, and 1 (6%) survived without hospitalization in ICU.

The subintensive, UTIC and emergency medicine, were considered as "intensive therapies" for the purposes of the study.

Of the patients who were positive for the Berlin criterion in which the reported thoracic ultrasound was available (5 total patients), one of these patients (admitted to the Molinette) was not positive for the 2-area Kigali ultrasound only. Two of these patients (both at Molinette) were not positive for 4-area Kigali or Kigali strict, always exclusively ultrasound.

If only patients with SpO2 / FIO2 <315 and SpO2 <97% + the ultrasound criteria are considered positive for Kigali, only 2 out of 5 patients (one hospitalized at Molinette, one at S.G.Bosco) test positive both in Berlin and al Kigali (2-area, 4-area, and strict).

One of these two patients (Giovanni Bosco, winter) ended up in intensive care and then died, the other (Molinette, summer) did not end up in intensive care and survived.

The number of patients positive for the Berlin criterion is low because most of the patients were not on PEEP (91% of the measurements).

Regarding the ultrasound associations with the various outcomes, 17 of the 2-area Kigali patients died (25% of the 69 2-area Kigali patients). Fifteen of the patients with 4-area Kigali died (26% of the total 57). Finally, 11 of the patients with “strict” Kigali died (26% of the 42 total). The association between Kigali and mortality is not significant for the 2 area Kigali (X^2 (1) = .11, p = .737), 4 areas (X^2 (1) = .48, p = .489), or “Strict” (X^2 (1) = .16, p = .687).

Regarding the association between Kigali and hospitalization in intensive care, we observe that 14 of the patients with 2-area Kigali were hospitalized in ICU (20% of 69 patients with 2-area Kigali). Twelve of the patients with 4-area Kigali were admitted to ICU (21% of the total 57). Finally, 8 of the patients with “strict” Kigali were hospitalized in ICU (19% of the 42 total). The association between Kigali and ICU admission is statistically significant for the 2-area Kigali (X^2 (1) = 4.22, p = .040), but not for the 4-area Kigali (X^2 (1) = 1.55, p = .213) or “strict” (X^2 (1) = 1.51, p = .219).

The direction of the association in this case is paradoxical and indicates that patients without 2-area Kigali were more likely to end up in TI. But simply because we speak of Kigali criterion only ultrasound and as such present in most of the patients observed who ended or did not finish in the ICU.

Therefore, the clinical association with ultrasound data is mandatory.

In fact, given that patients with SpO2 / FiO2 <315 and SpO2 <97% are considered positive for Kigali instead, we observe that 12 of the patients positive for 2-area Kigali have died (29% of the 31 patients who met the criteria), 11 of the 4-area Kigali positive patients (42% of the 26 total), 7 of the 'strict' Kigali positive patients (35% of the 20 total). For these patients, the association between Kigali and mortality is significant for the 2-area (X2 (1) = 5.21, p = .023) and 4-area (X2 (1) = 6.14, p = .013) Kigali, but not for the "strict" (X2 (1) = 1.28, p = .258). In fact, in the latter there is currently not a sufficient number to achieve significance.

Following the same criteria, it is observed that 7 patients with 2-area Kigali (23%), 6 with 4-area Kigali (23%), 5 with "strict" Kigali (25%) were admitted to intensive care. The association between Kigali and hospitalization in intensive care is not, in this case, significant either for the 2-area Kigali (X2 (1) = .12, p = .734), nor for 4 (X2 (1) =. 04, p = .851) nor 'strict' (X2 (1) <.001, p = 1) (Figures 28 Considering only the negative patients both in Kigali (2 areas) and in the Berlin criterion (21 patients), it is observed that 3 (14%) died without access to intensive care, 1 (1%) was hospitalized in ICU and is died, 9 (43%) survived without ICU hospitalization, and 8 (38%) survived ICU hospitalization. Access to ICU and mortality are not associated to a statistically significant extent (X2 (1) = .06, p = .810).

Discussion

Strengths and limitations

The laborious and punctual data collection, including variables at the patient's bed in possible continuous change, easily influenced by confounders not always linked to the respiratory function alone, certainly represented one of the limitations of the study, however reflecting what is reality in a transparent way of several hospital areas, other than intensive care, provided instead of continuous monitoring.

The aids used to provide FiO2 were various, in different settings, which increased the external validity of the results and can be extended to rural contexts, but it certainly made it difficult to accurately quantify the ratios required (for example SpO2 /FiO2 with the use of nasal cannulas with flows above 5 liters / min, which by definition can incur variations in the effective FiO2, or even patients who have used HFNC as a device, in which the uncertainty in the degree of PEEP used has not made it possible to satisfy the Berlin criteria).

The results obtained indicate that the findings of hypoxemia, high respiratory rate and reduced SpO2 / FiO2 ratio correlate with the main outcomes of mortality, need for intensive care and longer hospital stay. Further analyses are however necessary to examine the role that these parameters could have in the diagnostic-therapeutic process of the hospitalized patient with acute respiratory failure, and to understand if and how the ultrasound examination of the thorax can assist the doctor in the management of this category of patients.

In the final hospital discharge diagnoses, many patients were labelled and discharged with the final diagnosis as simple respiratory failure, even when these, followed over time, fell within the more detailed Berlin (and Kigali) criteria definition for ARDS (which may have contributed to underestimate the ARDS real incidence rates).

The very advanced average age of the population under examination, which mirrors hospitalization in the Western world (due to the increasing number of aging population) has meant that the causes of respiratory failure were often mixed and that it was sometimes possible

to interfere as described by the various studies in the diagnostic delay of ARDS in the 'span of the week under examination and therefore the delay in the use of ventilation, conditions clearer in the young patient with known predisposing factors.

Furthermore, the centralization of admission of patients that represent cases of trauma and major burns in the CTO trauma reference centre in Turin, mirror Turin hospital reality. The trauma centre (CTO) patients were not included in the study, which has certainly constituted a bias, very often excluding these pathologies known to be associated with ARDS and involving even younger patients, that could fit our eligibility criteria and could be possibly enrolled in our study.

It was not possible to obtain ultrasound data in all 12 projections for all 7 days for all requited patients. Both due to the possibility of lack of consent to be assessed daily, and due to various practical obstacles, contemplated in the data collection of the study design, which, however, also reflect the daily clinical reality. Twelve projections turned out to be complete in order to explore most of the sub pleural areas of the lung parenchyma and desirable for future comparisons with gold standard imaging, but objectively it was difficult to perform daily scans due to the daily ward activity. Studies with simpler formulations (for example with 6 projections, already tested) could be desirable.

Furthermore, our study, unlike the study by Riviello et al, did not contemplate the use of echocardiography for the purpose of excluding cardiogenic causes, but only used the lung projections described.

In the population examined, few patients, even if analysed in both the summer and winter seasons, reached the complex Berlin criterion, precisely due to the lack of ventilation with positive end-expiratory pressure (PEEP). This highlights the simplicity, reproducibility and usefulness of the Kigali criterion, that has allowed us to have few terms of comparison between the two criteria, despite the attempted large number of studies.

In centres such as the San Giovanni Bosco Hospital, in the face of the well-known greater boarding time in the DEA compared to the Molinette Hospital, it was decided to enrol patients also in the ED setting, which may have contributed sometimes to influence the patient consent to the study, types of care, nursing and therefore indirectly influenced patients' outcomes.

Being part of a bigger multicentre study that comprises different realities it is possible that when the Italian data are combined with data from Canadian centres there will be a difference in terms of both the possibility of data collection and in terms of the intensity of care setting with the same designation for the purpose of the database, but also with different assistance and intensity (concept of Canadian vs Italian Medical ICU, concept of "starting palliative care" in the two hospital realities, overlap of hospital surgical departments with Canadian "PACUs").

The main limitation of the study, however, remains represented by the sample size, insufficient for the execution of all the desired statistical analyses in order to compare the diagnostic accuracy of the two methods in enrolled patients.

The presence of CT images available at the moment was not so numerous for the recruited patients, especially for the less critical ones, making it necessary to complete the total data collection for diagnostic accuracy measures.

Further data collection and database revision will also allow to establish the agreement in the attribution of the Kigali criterion between two expert reviewers and if they disagree, a third expert will be included to revise all scans. At the moment this data is not the subject of a thesis, because the LUS scans still need to be interpreted by two expert ultrasonographers, as described in the protocol.

The "NITWA ARDS Study" was born in the North American and European reality in the light of the results obtained in Kigali, Rwanda, with the aim of determining whether a 'simplification' of the diagnostic determination of ARDS could improve its identification and early treatment even in contexts with limited health resources and in wards with less care intensity, for timely intervention.

The study conducted in Turin in the two hospitals Città della Salute e della Scienza and San Giovanni Bosco Hospital, during the summer season of 2019 and winter of 2020, screened 872 patients and enrolled 146, mostly male, mainly hospitalized in an emergency regime for diseases of medical relevance.

Within the group of 872 patients, the 146 hypoxemic patients enrolled already showed characteristics of frailty at the anamnestic analysis, presenting an average age over 70 years and various comorbidities, in particular of the respiratory type, and, in a minority of cases, taking home oxygen therapy even before hospitalization.

The study procedures were well tolerated by the patients, with a generally very high rate of bedside thoracic ultrasound, but only 63% for exactly all 7 days (or for discharge and death before the end of that period. or for lack of consent on some of the days, sometimes linked to worsening clinical conditions or pure intolerance to the procedure). Only 21 out of 91 patients (23%) have all 12 ultrasound projections for all measurement days, in agreement with clinical reality, suggesting that fewer projections would be desirable to compare and reproduce the method, with the possibility however to highlight fewer pathological findings, and not being able to explore exactly all the subpleural areas. Very few patients have encountered adverse events during the ultrasound, apparently not attributable to it.

The presence of hypoxemia expressed as the SpO2 / FiO2 ratio was significantly associated with an increased mortality, a higher transfer rate in intensive areas (intended as intensive and subintensive care units) and longer hospital stays, in agreement with the fact that this ratio represents one of the main parameters for judging the physiopathological function for patients. The detection of a high respiratory rate, on the other hand, unexpectedly showed very low variability and a significant association with mortality alone, but not with access to ICU, a factor that may however be linked to the limits of the study and the data collection and could be potentially influenced by other confounders.

At the end of hospitalization for both hospital centres, in discharge diagnosis in the medical records (following the criteria of the ICD-9-CM manual), 57% of patients received a diagnosis of respiratory disease (mostly represented by COPD and pneumonia and from the category "not otherwise specified ") and only 3% of ARDS (4 patients in total, 1% at the San Giovanni Bosco Hospital and 6% at the Molinette Hospital), slightly deviating from the expected figure of 4%, present in the study protocol, based on previous available literature.

With the review of the data collected, however, focusing on the attribution of the Berlin criteria for each patient, it was shown that the percentage was higher than that of the simple exit

diagnosis, reaching 11% of the total for the two centres (in particular with most of the cases at the Molinette Hospital in the winter season, for which ultrasound data are not available at the moment).

The mortality of these patients that fulfilled the Berlin criteria was 37% (6 patients died out of 16 patients in total).

On the other hand, applying the complete Kigali criteria (patients with SpO2 / FiO2 <315 for sato2 <97% and ultrasound criteria divided into three subgroups) it was observed that the number of patients out of the total of 91 ultrasound scans available was even greater: 31 patients (34%) for the two-area Kigali, 26 patients (29%) for the 4-area Kigali and finally 20 patients (22%) for the more complex “strict” Kigali.

The mortality of Kigali positive patients was 29% in 2 areas, 42% in 4 areas and 35% for “strict” Kigali, respectively.

Of 5 patients positive to the Berlin criterion and comparable with the Kigali criterion for the availability of ultrasound reports, 2 had positive results in all three types of analysis of Kigali areas (a 2, a 4 and "strict").

The discrepancy in the remaining three cases can be attributed in part to the impossibility, especially on the most critical patients, to be mobilized and to explore all the lung fields required to assign the scores accurately.

It should be emphasized, however, that the high percentage of presence of pleural effusion, strongly associated with areas reported as "consolidations" but often indistinguishable of a truly thickened nature or simply consensual atelectasis, may have led to overestimating the assigned Kigali scores.

Most of the patients did not reach the Berlin criterion, since the criterion of the presence of PEEP was missing at the observation, underlining the complexity of these criteria and the often inability to intercept the critically ill patient in an early manner compared to the Kigali criteria of simpler applicability in the various ward settings, even if not intensive, and by country. The Berlin criterion therefore remains an "ICU diagnosis" as described in the literature. Furthermore, the low percentage of ARDS assigned as the final diagnosis (ICD-9-CM) reflects the incompleteness of some data that can be obtained only from medical records regarding this complex syndrome underlying other pathologies, more often simply reported on discharge by the clinician as " respiratory insufficiency ", therefore without a" precise prognostic label ", as well as diagnostic, with the risk of underestimating the picture and delaying therapeutic intervention.

As an important future perspective for this study would be the fulfilling o the REDCap Database with the interpretation of the lung scans.

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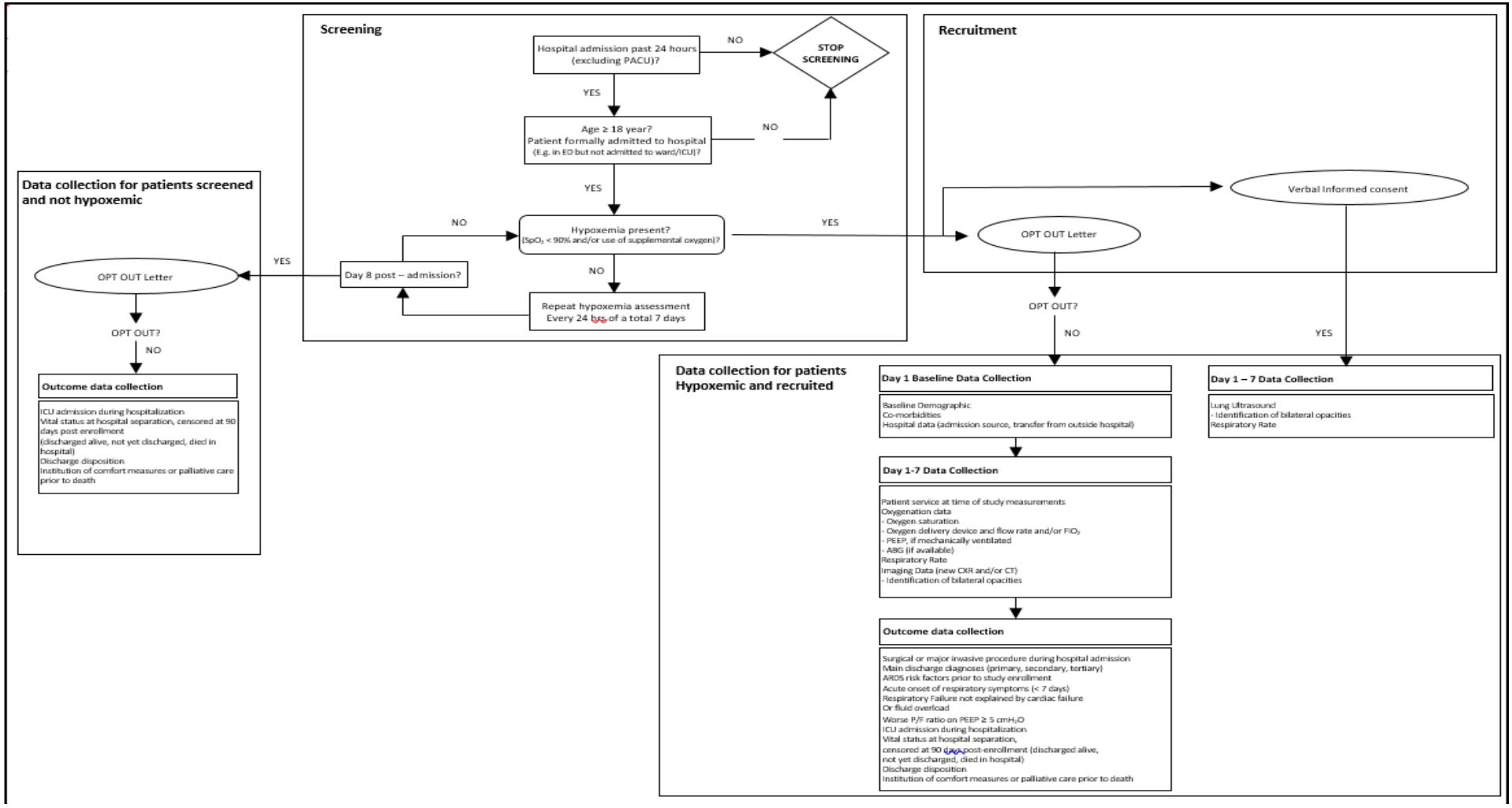
Supplementary material

Figure 17. Study flow chart



Overall interpretation and final conclusions

As technologies develop it can be expected that the ultrasound devices are going to be more sophisticated and more affordable and accessible, not only for Emergency medicine physical, but also for all medical trainees. It is very probable that the fields of applications of POCUS are going to grow and develop. It is very important always to have in mind that POCUS is applied by the bedside with the main aim to answer to a specific question that a clinician has posed. With these answer is becoming easier to the clinician to direct therapy, guide some procedures and come to the diagnosis.

More accurate assessment clinically is possible and it is a tool to see what happens inside the body. And better triage level up to transfer patient to more appropriate facility. New clinical challenges like medications, specialized treatments and visit highly acuity patients at home. POCUS is going to be ubiquitous and probably durability and quality will improve. Artificial intelligence is rapidly improving the capability of these machines to give us accurate and useful measurements with which we can improve patient care.

POCUS is an adjunct to the clinical assessment and it does not replace any part of it. POCUS has an amazing ability to prove the diagnostic accuracy, expedite the time to diagnosis and treatment and potentially avoiding the pitfalls of ionizing radiation and costs.

Aside from the positive effect of POCUS on the healthcare of patients, the better performance with POCUS may have great impact also on societal level by reducing health care costs of hospital stay, and reducing mortality rates. POCUS enabled identification of few patients that have been missed when using only the SOC and establishing/ formulating the right diagnosis.

CLINICAL IMPLICATIONS: POCUS adjunction can aide the diagnostic process and the treatment decision in the ER when conventional imaging techniques and work up does not exhibit a clear diagnosis.

In this thesis, POCUS mostly served as diagnostic adjunction and demonstrated satisfactory diagnostic values in different patient populations. Our findings suggest that the use of POCUS in patients with syncope and in acute dyspnoeic patients presenting to the ED has increased diagnostic accuracy and decreased the rate of misdiagnosed patients in comparison with the standard of care. We also want to point out that LUS appears to be associated with reduced LOS and might accelerate ADHF diagnosis and improve treatment and quality of care in dyspnoeic patients. In patients with syncope the use of POCUS has enabled correct diagnosis and stratification of patients with non-high risk syncope in comparison with the SOC. Using the Kigali definition, where lung ultrasound is used together with other clinical parameters in patients with hypoxemia, we observed that the use of LUS may help in “simplifying” the diagnosis of ARDS and with that may contribute to a more rapid and accurate final diagnosis of ARDS and shorten the waiting times for these patients. Based on our findings, we would like to highlight the substantial role of the use of different modalities of POCUS when added to SOC routine evaluation in assessing patients with acute dyspnoea, syncope or in hypoxemic patients and we would like to encourage ED physicians worldwide to incorporate POCUS as an adjunctive step to the SOC in their daily practice. In other words, POCUS is becoming the

“stethoscope of the future” of the bedside diagnosis for many medical conditions and diseases and it is widely used in everyday medical practice.

In acknowledgement with existing clinical guidelines, the role of POCUS is invaluable in the clinical decision-making process and merits to be incorporated in official recommendations. The application of POCUS in ED is additionally supported by our results as with other evidence that are emerging every day from the medical literature. All this evidence-based results of implementing POCUS as an ultrasound stethoscope in ED by a prudent clinician would inevitably guide to an excellent and advance patient care.

One of the future perspectives may be to conduct cost-effectiveness analysis in order to see if POCUS is “expensive” to use. Another perspective should be the fulfilling of the REDCap database with the interpretations of the LUS scans for the winter period for Molinette hospital. This may be useful because in this way we can calculate the incidence also according to Kigali definition for ARDS. That could lead also to possibility also to evaluate the diagnostic accuracy of LUS in comparison with CT as gold standard. The completion of the database will allow to make analysis also to the whole data from this multicentre study, where we can expect to see interesting results. However, further studies are necessary in order to validate our results.

Anyhow, we should always remember with the great clinical power of using POCUS, comes also a great challenge and responsibility to use POCUS wisely. That’s why physicians should attentional use POCUS.

Clinical medicine is tremendously complex and our mind just cannot integrate every piece of evidence.

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