ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ»

(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)

Μεταπτυχιακή Διπλωματική Εργασία

«Εκτίμηση Συμφόρησης στην Καρδιακή Ανεπάρκεια»

υπό

Μιχαηλίδη Ελένη

Ειδικευόμενη Καρδιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Καρδιακή ανεπάρκεια – Καρδιο-ογκολογία – Καρδιαγγειακή αποκατάσταση»

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(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)

«Congestion Estimation in Heart Failure»

Larisa, February 2024

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΕΛΕΝΗ ΜΙΧΑΗΛΙΔΗ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2024

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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Τίτλος εργασίας στα αγγλικά: Congestion Estimation in Heart Failure

Ευχαριστίες

Θα ήθελα να ευχαριστήσω ιδιαίτερα τους επιβλέποντες καθηγητές μου, κύριο Σκουλαρίγκη και κύριο Ξανθόπουλο, για όλη την καθοδήγηση και τις συμβουλές στην διάρκεια της έρευνας και της σύνταξης της μεταπτυχιακής εργασίας. Παράλληλα ευχαριστώ ιδιαίτερα τους φίλους και την οικογένειά μου για την στήριξη που μου παρείχαν στην προσπάθεια αυτή.

Μιχαηλίδη Ελένη

Εκτίμηση Συμφόρησης στην Καρδιακή Ανεπάρκεια

Περίληψη

Η Καρδιακή Ανεπάρκεια αποτελεί αδιαμφισβήτητα ένα από τα συχνότερα και σημαντικότερα ιατρικά προβλήματα της σημερινής εποχής, επηρεάζοντας σε μεγάλο βαθμό την ποιότητα ζωής των ασθενών καθώς και το προσδόκιμο επιβίωσης. Ο επιπολασμός όπως και η θνητότητα της συγκεκριμένης νόσου ακολουθούν ανοδική πορεία τα τελευταία έτη. Η συμφόρηση αποτελεί ένα από τα βασικά αντικείμενα προς έρευνα στον τομέα της Καρδιακής Ανεπάρκειας, καθότι σχετίζεται με τις επανανοσηλείες και την έκβαση των ασθενών. Η παρούσα βιβλιογραφική ανασκόπηση επιχειρεί να παρουσιάσει την πλειοψηφία των διαθέσιμων μεθόδων σχετικά με την ακριβή εκτίμηση της συμφόρησης σύμφωνα με τη διεθνή βιβλιογραφία. Για την έρευνα χρησιμοποιήθηκε η μηχανή αναζήτησης Pubmed. Η απουσία ενός ενιαίου δείκτη ικανού να αναδείξει και συγχρόνως να ποσοτικοποιήσει τον βαθμό συμφόρησης των ασθενών παραμένει ένα βασικό πρόβλημα για την επίλυση του οποίου διάφορες μέθοδοι επιστρατεύονται ώστε να οδηγήσουν σε ένα πιο ακριβές αποτέλεσμα. Συγκεκριμένα, η κλινική εξέταση, τα εργαστηριακά ευρήματα, οι απεικονιστικές εξετάσεις, ο καρδιακός καθετηριασμός καθώς και διάφορες σύγχρονες τεχνικές τηλεϊατρικής αποτελούν τα συχνότερα χρησιμοποιούμενα μέσα. Οι αναφερόμενοι αυτοί τρόποι θα αναλυθούν και θα συγκριθούν περαιτέρω στην πορεία της εργασίας.

Λέξεις - κλειδιά: Συμφόρηση, Καρδιακή Ανεπάρκεια, βιοδείκτες, απεικόνιση.

Congestion Estimation in Heart Failure

Abstract

Heart Failure depicts a crucial health problem of recent years, severely limiting the quality of life as well as the longevity of the affected population. As the life expectancy constantly increases so does the number of Heart Failure patients and associated deaths. Congestion is of paramount importance in Heart Failure as it is a major determinant of the outcome of patients. More specifically, residual congestion is strongly correlated with rehospitalizations and mortality. This review aims to present and compare the main available methods of assessing and quantifying congestion in Heart Failure patients according to contemporary literature. By collecting recent data through the Pubmed Search Engine, different ways of estimating congestion are presented. A significant challenge regarding Heart Failure patients is that despite the tremendous technological improvement of the last decades, there is still not a single method to accurately identify the level of congestion. Due to this, multiple tools are utilized and the results of each method are compared and combined. More specifically, clinical examination, laboratory tests, imaging modalities, cardiac catheterization and the new opportunities offered through telemedicine are some of the fundamental techniques which provide an insight regarding the volume status of patients. Some of these modalities have not yet been employed in clinical practice, while others such as Chest X-ray or Natriuretic peptides are routinely ordered when dealing with a Heart Failure patient. In this literature review, these methods will be explored and analyzed alongside their drawbacks and benefits.

Key words: Congestion, Heart Failure, biomarkers, imaging.

Πίνακας Περιεχομένων

INTRODUCTION

Definition and Classification of Heart Failure

Heart Failure (HF) is a condition characterised by the inability of the heart to meet the oxygen demands of the organism, due to ventricular impairment which is either structural or functional in origin. Among some common causes, ischaemic heart disease, chronic uncontrolled hypertension, valvular heart disease, myocarditis and cardiomyopathies are included (1). Nowadays, HF is a global pandemic and in 2017 it was estimated that approximately 64 million people were diagnosed with this clinical syndrome worldwide. The prevalence of the disease is 1-3% in the general adult population and is expected to rise further due to the advancements in life-saving treatments thus improved overall survival. Although the prognosis of the disease has been improved over the years, the mortality remains high. More specifically, the 1- and 5-year mortality risks are between 15-30% and 75% respectively. Finally, it is important to underline that the expenditures on healthcare systems due to HF constantly increase and it is estimated that in 2030, the healthcare costs in the USA will reach 69.8 billion dollars (2).

This clinical syndrome is traditionally classified according to the Ejection Fraction (EF), which is the proportion of blood being ejected by the left ventricle (LV) during each heartbeat. More specifically, left ventricular EF (LVEF) is the ratio between the stroke volume and the end diastolic volume of the LV and patients can be broadly classified into four categories. According to the American Heart Association, the first category is the HF with reduced ejection fraction (HFrEF) which is characterised by LVEF $\leq$ 40%, while an LVEF $\geq$ 50% is considered as HF with preserved EF (HFpEF). Patients with an LVEF between 41- 49% belong to the category of HF with mildly reduced EF (HFmrEF) and lastly patients who had an EF $\leq$ 40% which increased to above 40% in a following measurement are classified in the category of HF with improved EF (HFimpEF) (5).

There are several definitions and classifications of HF and the aforementioned one is the most commonly used. However, it is important to mention that there is a lot of criticism against the implication of a single biomarker such as EF in the stratification of patients

with HF. As it is stated above, HF is a syndrome, and the progression of the disease is highly dependent on the structural and functional alterations of the ventricles which result in a spectrum of several phenotypes that may have overlapping features. Factors that are associated with the development of these distinct phenotypes include gender, age, risk factors such as hypertension, obesity and particular comorbidities (i.e. chronic kidney disease) (6). Although EF is a very useful parameter in the assessment of HF patients, other factors should also be taken into account since each patient is a separate entity with their own comorbidities and risk factors that contribute to the overall disease prognosis.

Apart from the grouping of patients regarding the EF, patients could also be classified according to the stage of disease. In fact, the stages of HF as presented in the ACC/ AHA are four, namely stage A in which there are patients at risk for developing HF, stage B which is the preHF phase, C for patients with overt HF accompanied with symptoms and finally stage D which represents the advanced stage of HF (5).

Pathophysiology of Heart Failure

In HF the heart muscle is unable to meet the metabolic requirements of the organism. At first, there is an initial event which causes the heart to malfunction and in order to maintain an adequate cardiac output several mechanisms of compensation develop. This event could be an infarction, an infection of the heart muscle, a heart valve disease, infiltration of the tissue or genetic mutations due to which abnormal proteins are produced leading to a dysfunctional heart muscle. In order for the cardiac output to remain constant and suffice for the metabolic demands of the various organs, the organism attempts to compensate by employing the Frank- Starling mechanism, activating the neurohormonal system and lastly through remodelling of the heart muscle (7, 8).

Mean Arterial Pressure (MAP), which indicates the pressure of perfusion, can be approximately calculated by multiplying cardiac output (CO) with total peripheral resistance (TPR). In cases of HF, CO is decreased leading to a decline in perfusion pressure. As the heart muscle cannot pump enough blood, the stroke volume (SV) drops

and the left ventricular end diastolic volume (LVEDV) rises. Due to this, left ventricular end diastolic pressure (LVEDP) also increases and thus the muscle fibres of the heart stretch further providing a near normal CO via Frank Starling mechanism (9). Regarding the Neurohormonal mechanism, as MAP declines, the Sympathetic Nervous System is activated, catecholamines are released which act both on the heart muscle and on the systemic circulation. This increases the force of contraction, the heart rate and causes vasoconstriction of the arterioles which increases TPR thus maintaining MAP. Additionally, the renin- angiotensin- aldosterone system (RAAS) gets activated due to the decreased renal perfusion and due to the activation of β1 receptors. The net effect of this activation is enhanced heart contractility and vasoconstriction, release of norepinephrine, reabsorption of sodium and water and excretion of antidiuretic hormone both of which result in an increase of the total blood volume and hence of stroke volume (9, 10).

Initially these mechanisms are particularly helpful; however, their long-term activation leads to further progression of HF. More specifically, due to the chronic stimulation, beta-receptors become less responsive and in addition, potentially lethal arrhythmias are provoked, the demands for oxygen of the myocardium rise considerably and remodelling of the heart muscle occurs (8, 11). The term remodelling refers to several alterations regarding the geometry, dimensions and heart's functionality after an insult. Some of the changes which take place include death of the myocardial cells, interstitial fibrosis and hypertrophy of some parts of the heart whereas others become atrophic (12, 13). All of the above mechanisms result in overload of the volume status, rapid heart rate, dyspnoea and a vicious cycle of constant worsening of heart function which results in poor perfusion of all organs.

Depending on the predominant side of the heart which malfunctions, corresponding symptomatology occurs. If the pathology mainly affects the LV, then the systemic perfusion is reduced as less blood is pumped during each cardiac cycle. Furthermore, the LVEDP rises leading to congestion of the pulmonary circulation. In order to withstand the high-pressure levels, the heart size alters resulting in an increased cardiothoracic index (CI) (11). If on the other hand the Right Ventricle (RV) is primarily affected, then

congestion of the systemic venous system ensues. It is worth mentioning that most of the times Right-sided HF develops in a person with Left-sided HF. As failure of the LV often causes pulmonary hypertension, the right ventricle cannot cope with the high pressures of the pulmonary system and its function deteriorates as well (14).

Congestion resembles one of the fundamental problems of HF patients given that it greatly affects hospitalisations, mortality and overall prognosis. Congestion in HF arises from the high filling pressures of the heart which result in fluid accumulation both in blood vessels as well as in the interstitial space (3). The stimulation of the Sympathetic nervous system causes redistribution of blood from the splanchnic compartment to the systemic circulation and the effective blood volume expands. As HF progresses, several decompensation episodes occur. Most of HF patients visit the Emergency Department due to the development of congestion related symptoms, while only a small percentage of HF patients require urgent medical assistance due to symptoms related with low CO (15, 16). Considering the aforementioned, the ability of early identification of congestion prior to an acute decompensation episode with the available tools is of paramount importance.

Clinical significance of congestion

Despite the advancement in the therapeutic management of HF, several people die and also the national economy is greatly affected, therefore further research is required in order to assess and manage patients more effectively. A hallmark of HF which greatly affects the prognosis of patients is congestion both systematic as well as pulmonary. Undoubtedly it is the leading cause of decompensation in chronic HF patients resulting in hospitalisation, thus it contributes significantly to poor prognostic outcome. The term «congestion» refers to the accumulation of fluid both in the interstitial and intravascular spaces due to high pressures in the heart chambers and inability of the kidneys to excrete sodium and water. The decompensation results in acute HF and the patient may present with several symptoms, however the severity of presentation varies (3).

Because congestion is strongly linked to poor patient's prognosis, it is of high importance to assess and treat patients with signs and symptoms of congestion before the development of decompensation. Additionally, a significant amount of people who are admitted to the hospital with acute HF are discharged despite the presence of residual congestion which may lead to rehospitalisation and death within a period of 6 months. Therefore, it is essential to emphasize on the importance of assessing and treating congestion prior to the development of acute HF. Also, in case the patient is hospitalized, correct assessment and monitoring is required prior to discharge in order to avoid any negative outcomes (4).

As previously stated, the ability to earlier identify and treat increased filling pressures in the vasculature of these patients due to decompensation of HF could potentially reduce rehospitalizations and improve prognosis. Some of the main ways of estimating congestion is by performing clinical examination and taking a thorough medical history of the patient, by employing imaging methods, measuring the level of several biomarkers and by performing right heart catheterization in extreme cases. This aim of this literature review is to present and compare the methods employed in order to assess and quantify congestion in HF patients according to contemporary literature.

METHODS

This literature review was conducted primarily based on PubMed search engine; however, other sources have also been employed. The following terms were used in the search engine: Heart failure [Title/Abstract]) AND congestion [Title/Abstract]) AND assessment [Title/Abstract]). The results were 391, however this literature review is mainly focused in the last 10 years between 2013 and 2023. By applying the above limitations to the initial search, the results were narrowed down to 298 articles. Additionally, two more searches were performed using the same terms as above and substituting the term assessment with imaging and biomarkers respectively. By applying the same criteria as above the results were limited to 151 and 132 respectively. The above articles were carefully screened, and the most relevant ones were analysed in this literature review.

DISCUSSION

CHAPTER 1 – Clinical Evaluation of Congestion

1.1 Symptoms of congestion

People with acute or chronic HF may present with several symptoms because the heart becomes unable to fill or eject the blood effectively. Difficulty in breathing is the most common complaint of these patients, however, it is neither sensitive nor specific for HF with the percentages being approximately 66% and 52% respectively (17). As the ability of the heart muscle to pump blood is limited in HF, fluid accumulates in the lungs where it passes from the vasculature to the interstitial lung space and the alveoli resulting in pulmonary congestion.

Dyspnoea often presents in three forms in HF. Firstly, a lot of patients complain about orthopnoea which is defined as shortness of breath when lying down and it is relieved by sitting up or standing. Orthopnoea is the result of an elevated preload to the malfunctioning heart chambers as the venous return increases by lying flat (3, 18). Regarding the results of the ESCAPE TRIAL, orthopnea had a sensitivity of approximately 86% for estimating increased filling pressures of the left- sided chambers (19). Another common form of dyspnoea is Paroxysmal Nocturnal dyspnoea (PND) which awakens the patient and is also relieved in an upright position. PND is often followed by acute pulmonary oedema in the subsequent days (18). These two forms of dyspnoea are indicative of HF (20). Moreover, shortness of breath on exertion frequently occurs in HF patients. Some other commonly referred symptoms are fatigue, chest discomfort, palpitations and exercise intolerance due to inadequate cardiac output. Furthermore, persistent cough and wheezing arise because of congestion in the pulmonary system (21). Patients with HF may complain of abdominal distention, ascites and pain in the right hypochondrial region as well as peripheral oedema resulting from impaired return from the venous vasculature (9, 22).

1.2 Signs of congestion

In addition, there are several signs in the clinical examination of HF patients which indicate congestion. The most specific sign is the S3 sound which is heard after the S2 as a result of the rapid filling of the non-compliant LV since the mitral valve opens and the diastolic phase begins (23). S3 sound depicts elevated diastolic pressure of the LV, above 15 mmHg, along with impaired systolic function of the ventricle and it can be heard at the apex of the heart by using the bell of the stethoscope (24). Although the S3 sound is remarkably specific regarding the acute decompensation of HF, its low sensitivity significantly limits its diagnostic accuracy (25). The article Back to Basics emphasizes the significance of clinical examination and the pretest probability for each part of the exam for HF patients in an emergency setting. According to this article, S3 sound has a sensitivity and specificity which ranges significantly in several conducted studies with the numbers being 32 -73% and 42 -99% respectively. Even though the ability to auscultate S3 sound varies among individuals its presence is an indicator of poor clinical outcomes. S4 sound, which is heard during the end of diastole, is associated with decreased compliance of the LV (24).

The level of jugular venous pressure (JVP) depicts another useful way of assessing congestion in HF. In a healthy individual the blood is returned from the systemic circulation by the vasculature of the venous system to the right atrium and then it is pumped through the right ventricle to the pulmonary system. Thus, the volume in the venous reservoir remains steady as there is constant flow. However, in cases of HF in which this mechanism does not work efficiently, pressure in the heart chambers increases and hence elevation of the pressure of the venous system occurs. As the internal jugular veins are in continuity with the superior vena cava which supplies the right atrium with blood, these vessels can be used as an indicator of the pressure in the right atrium. This can be done by inspecting the jugular veins and assess the degree of expansion (26, 27). Assessment of JVP through clinical examination is neither sensitive nor specific with the figures being 57.3% and 43.6% correspondingly (3). These low figures could be partly attributed to the low levels of practice in the current era of rapid technological development in which less emphasis is given in estimating volume status through a methodical clinical examination.

According to Harada et al, an elevated JVP correlates with high LVEDP. More specifically, if JVP is present, then the Pulmonary capillary wedge pressure (or PCWP) is over 18 mmHg with a sensitivity and specificity of approximately 80%. In addition, clinical estimation of the volume status of a patient is accurate in guiding pharmacologic treatment and findings are similar to the fluid status measured with right heart catheterization (24). In one of the largest studies conducted concerning the role of physical examination in HFpEF patients in recent years, which examined people enrolled in the PARADIGM- HF study, similar results were obtained. In fact, JVD is a sign of increased filling pressures of right heart chambers and is a common finding in patients with increased wedge pressure. In addition, its prognostic value remains unchanged despite the initial Body Mass Index (BMI) levels (28).

Other common signs indicating congestion include sinus tachycardia, laterally displaced apical impulse due to the enlargement of the LV and hepatosplenomegaly (29). Another useful marker of congestion is ankle oedema although it can be seen in a range of different pathologies such as hepatic and renal disorders, malabsorption or it could be the result of usage of medicines such as calcium channel blockers. Regarding auscultation, bilateral inspiratory crackles or rales could be heard at the lung bases as a result of congestion of the interstitial lung space, but it is important to mention that this sign might be absent at the initial event of decompensation or in a chronic condition. Nevertheless, as the aforementioned markers often appear late and the patient has to be hospitalised for decongestion, imaging procedures are considered by many more accurate (17).

The ESCAPE Trial emphasized on the role of History and Physical Examination (H&P) in evaluating the volume status of patients with Advanced HF. This survey concluded that increased JVP and the symptom of orthopnea are markers of an increased PCWP value and hence of congestion. Moreover, the volume status of the patient estimated by H&P is accurate and is also a prognostic indicator (19). As it can be derived from the above, the role of physical examination in the assessment of congestion in HF cases is still vital and accurate nowadays, thus doctors should be trained in being able to obtain a thorough H&P in this era of tremendous technological improvement instead of relying solely on other non- invasive methods such as biomarkers or imaging.

1.3 Body Weight Changes

Body Weight can also serve as a tool for monitoring congestion in patients with HF. As the volume status of these patients expands due to the reabsorption of water and sodium, changes in body weight are indicative of hemodynamic alterations. If the body weight of a patient is daily measured, the noted changes are usually associated with the fluid status. In contrast, conditions such as HF related cachexia result in observable alterations of body weight in longer time periods (e.g., month) (18). Chaudhry et al suggested that by obtaining daily the body weight of HF patients, critical periods for HF decompensation could be earlier identified and managed accordingly in order to prevent hospitalizations (78).

CHAPTER 2 - Imaging Methods

2.1 Chest X- Ray

Chest X-Ray (CXR) is a relatively fast, low- cost and easily accessible imaging technique, frequently ordered at the Emergency Department when dealing with dyspnoeic patients. The main findings which appear progressively throughout the course of congestion are firstly the blood flow redistribution from the lower to the upper lung lobes with increased diameter of the veins of the pulmonary system and then the enlarged hilar structures. Subsequently, Kerley A and B lines appear because the interlobular septa fill with fluid with the subpleural space following. These findings occur due to the rise of hydrostatic pressure in the capillary vessels. As the fluid builds-up and fills the alveoli, central, symmetrical opacified regions develop. Another sign of HF in a CXR is the enlarged cardiac silhouette. It is worth mentioning that these radiologic markers of clinical congestion often appear before symptoms develop and might also still be seen for some time after the healing of the patient (30-32). Oedema of the interstitial space, fluid in the pleural cavity and congestion depicted in the pulmonary vasculature are considered the markers with the highest specificity in patients with acute HF.

In addition, CXR aids in excluding other pathologies with similar clinical presentation including dyspnoea (33, 34). However, CXR is not very sensitive regarding the detection of pulmonary oedema as it appears negative in one fifth of the patients who actually have pulmonary oedema (34). Moreover, it is not considered an accurate method for diagnosing HF, particularly if the patient has coexisting lung disease (35). According to Pirrotta et al, CXR is an accurate tool in evaluating patients with acute HF in an advanced stage; however, early signs of congestion in chronic patients are often missed and therefore the diagnosis as well as the decongestion therapy could be delayed due to this (17).

Furthermore, HF should not be excluded in a patient without signs of congestion in the chest radiograph (36). In a study conducted by Berman et al, which investigated the possibility of HF in patients with normal BNP levels but with radiographic evidence of congestion concluded that if both tests were negative then HF could be more accurately ruled out. If on the other hand BNP was negative in patients with concomitant risk factors such as higher BMI, complicated Diabetes Mellitus or chronic HF, then CXR alone could aid in the diagnosis of HF (37).

A useful way of assessing congestion in a CXR is the Congestion Score Index (CSI). Concerning this scoring system, the pulmonary system is divided in six areas and each area is graded from 0, if there is no congestion, to a maximum of three for presence of profound pulmonary oedema in the alveoli. Then the scores in all different areas are summed up and divided with six. This investigation showed that CSI scoring system of a CXR could identify acute HF in patients presented with acute dyspnoea and is considered comparable in magnitude to the diagnostic worth of BNP measurement. Furthermore, considering patients who were hospitalised for acute HF, if CSI is combined with the results of Estimated Plasma Volume Status (ePVS), then those patients with high risk of death during hospitalisation due to congestion could be identified and treated accordingly. EPVS is an indicator of LV filling pressure and of congestion in the pulmonary system, and it can be calculated by this equation: ePVS = $\frac{100-Ht(\%)}{Hb\ (g/dl)}$ (35).

CXR is certainly a cornerstone of investigation in patients presenting with acute dyspnea; however, it is worth mentioning that noteworthy discrepancy was observed in the interpretation of pulmonary congestion between doctors working at the emergency unit and radiologists. Furthermore, there is significant variation in the values of sensitivity and specificity of CXR with the figures ranging from 14- 68% and 53- 96% correspondingly with regards to literature results (38).

2.2 Ultrasound

The gold- standard technique both for identification as well as follow-up of HF patients in a non- invasive manner is the ultrasound. This modality is widely available, with a reasonable price, without ionizing radiation exposure and is also available in a portable form (39). Echocardiography aids in the investigation of the cause of HF and also helps categorizing patients with regards to the EF (4). The main ultrasound methods for detection and estimation of the level of congestion include the examination of the heart, lungs, renal system and venous system (40). Echocardiography is very useful both in the acute setting and also during follow-up of HF patients in order to guide therapeutic decisions and precisely assess the heart. However, some of the main disadvantages of a thorough echocardiography evaluation is the need for specialized and experienced personnel and that it is also time-consuming hence it cannot be repeatedly performed throughout the hospitalization period of patients.

2.2.1 Transthoracic Echocardiography

Transthoracic Echocardiography (TTE) is a very useful tool which enables physicians to approximately estimate the EF, thus, categorize patients accordingly. Moreover, structural and functional heart problems could be diagnosed such as congenital abnormalities, malfunctioning of the valves of the cardiac muscle and possible effusions. The LV filling pressures can be estimated via several measurements, some of which are the motion of the annulus of the mitral valve, mitral inflow and left atrial volumes. More specifically, the ratio of the velocity of the wave initially filling the LV at early diastole

(E) to the velocity of the wave arising from atrial contraction during late diastole (A) is indicative of the pressure gradient through the mitral valve. In case this ratio (E/A) is above two with a deceleration time of the E wave below 160 msec then the pressure of the LV is high. On the other hand, in case the transmitral gradient pressure is low, with E/A ratio below or equal to 0.8 and E velocity below 50 cm/s, then filling pressures are within normal limits.

Lastly, for figures ranging in between further criteria should be employed, including E/e', peak regurgitation velocity through the tricuspid valve (TR) and the maximum volume index of the Left Atrium (LA). Regarding E/e' ratio, e' represents the velocity of the mitral annulus early during diastole. A ratio above or equal to 14 indicates increased filling pressure of the LV. Concerning the maximal volume index of the LA, a value above 34 mL/m^2 in 2D echocardiography implies enlargement of the LA due to the chronic elevated LV filling pressures. Finally, peak TR velocity exceeding 2.8 m/s is another measurement indicative of high filling pressures. Accurate information can also be obtained about the right side of the heart, for example whether pulmonary hypertension, dysfunction of the right part of the heart and severe tricuspid regurgitation are present. Overall, echocardiography is considered an accurate way of estimating the pressure in the LV with good correlation with the results obtained through invasive techniques such as right heart catheterization (4, 40, 41).

2.2.2 Lung Ultrasound

Lung Ultrasound (LUS) is an accurate and frequently used techniques of estimating congestion in HF. The main findings associated with cardiogenic pulmonary congestion in a LUS examination include vertical echogenic lines called B lines or comet- tails. Specifically, these lines are artifacts arising due to the accumulation of fluid adjacently to air-filled structures as water and air tend to have different acoustic impedances. In a healthy lung, the number of B lines is rather small. In order to perform this examination, chest should be examined both anteriorly and laterally, by scanning four intercostal spaces in both sides of the thorax. For the test to be considered positive, at least three lines are required in two different areas at each side.

Nonetheless, a positive test might as well indicate interstitial lung disease, therefore, further testing such as examining the function of cardiac chambers with the same probe is required in order to confirm the cardiogenic origin of B-lines. Interstitial fibrosis due to covid- 19, acute respiratory distress syndrome and pneumonia affecting the interstitial space are among some common causes of B-lines with pulmonary disease origin. The clinical usefulness of LUS could be employed when chronic obstructive lung disease (COPD) and acute HF should be differentiated. In fact, the difference in LUS findings in COPD patients is usually the absence of B-lines in contrast to the patients with cardiogenic pulmonary congestion.

Finally, B-lines are also highly important when assessing residual congestion of the lungs and deciding whether further treatment is needed (30, 39). In addition, these comet- like lines in LUS also depict a useful prognostic tool. Particularly, the more the B-lines are, the higher the risk for acute HF, hospitalisation or death in the following 6 months will be, regardless of age, sex or NYHA (New York Heart Association) score. LUS can significantly aid in the identification and monitoring of congestion as well as in guiding treatment both in the inpatient and outpatient setting. In fact, 30 and over B- lines depicted in the LUS at discharge is an indicator of residual congestion and of a poor outcome regarding both rehospitalization and also mortality in the short term (42). Additionally, the amount of B lines declines with decongestive therapy; however, it also changes with position which should thus be kept steady throughout follow-up evaluations. As the results of this review were based on small sample sizes, further investigation is required (43). An optimal position which enables the visualization of both the anterior and posterior parts of the chest is the semi-supine- standing (17).

Overall, LUS aids in estimating the volume status of the patient in a non-invasive manner provided that physicians are highly trained in performing this examination (38). Some of the main drawbacks of LUS is that even though it is a quite sensitive method, B lines are often present in interstitial diseases of the pulmonary system and can be differentiated only through a multimodal assessment consisting of laboratory, imaging and clinical examination (41). In several studies LUS was compared with CXR regarding congestion evaluation in HF cases. Maw et al conducted a systematic review which compared the

diagnostic accuracy of point of care LUS and CXR in adults with symptoms of acute HF. This survey concluded that LUS is considered more sensitive than CXR and of similar specificity in diagnosing cardiogenic pulmonary edema in these patients. Moreover, LUS is considered an easy entity for physicians to learn performing it and to be able to interpret the results (34). Regarding this comparison, Pirrotta et al, showed that even though both of these techniques are accurate in patients presenting with acute HF symptoms, LUS is more accurate and better in estimating the prognosis in chronic HF patients (17). However, CXR provides a panoramic image of the thoracic cavity for a more direct and detailed investigation (30).

2.2.3 Inferior Vena Cava Ultrasound

Imaging of the inferior vena cava through Ultrasound is also particularly useful in estimating the volume status of patients as well. The main parameters which are assessed are the diameter of the inferior vena cava and the corresponding change noted with respiration. In fact, if the diameter of the inferior vena cava is less than 21mm and with a collapsibility of above 50% during inspiration, then the pressure of the right atrium is within normal limits and this finding is associated with better outcomes (4, 39, 40). Generally, inferior vena cava is considered a significant marker of subclinical congestion in the systemic circulation (41). It is worth mentioning that approximately one out of every five HF outpatients without overt clinical symptomatology or signs of congestion have an inferior vena cava of increased diameter and the higher the inferior vena cava diameter, the larger the size of the LA, the higher the Natriuretic Peptide (NP) levels and lastly the greater the likelihood of early occurring cardiovascular incidents irrespective of the EF (39).

2.2.4 Renal System Ultrasound

The Renal System is another area which could be explored through Doppler Ultrasound methods in order to provide valuable insights regarding the congestion level of HF patients. More specifically, as the Central Venous Pressure (CVP) increases, the estimated Glomerular Filtration Rate (eGFR) decreases as congestion of the kidneys occur. In fact, when CVP is normal the blood flow observed through the renal veins is continuous throughout the cardiac cycle. As the level of congestion increases, discontinuous flow is firstly observed which is initially biphasic (both in systole and diastole) and then becomes monophasic occurring only during diastole (39, 41). This pattern indicates elevated right atrial pressure and an increased risk of death and hospitalization due to HF (44).

The role of ultrasound was also explored in a study regarding the assessment of congestion in various organs in outpatients with HF. According to the results of this research, the signs of congestion are as follows: 1) at least four B lines in the lung 2) not continuous renal blood flow in the venous system and 3) an inferior vena cava with a diameter of at least 21mm. Moreover, patients who had two or more of the aforementioned signs did have the worst prognosis and those without any signs of congestion had indeed a very good prognosis (45). These findings are consistent with the results of a systematic review published in 2017, which investigated the role of LUS in the assessment of congestion in HF patients both in the emergency setting as well as in chronic cases (43, 45).

2.3 Computed Tomography

A scan of the chest with Computed Tomography (CT) provides valuable information concerning the volume status of a HF patient. Nevertheless, it is not widely used due to several reasons such as high expenses, significant exposure to ionizing radiation and lastly limited availability of this equipment. CT scan of the pulmonary system can easily

identify build- up of fluid in the thoracic cavity (41). Miger et al carried out a prospective study investigating the main signs indicating acute HF in patients presenting with dyspnoea of acute onset. According to the obtained results, an enlarged heart, thickening of the interlobular septa on both sides of the thorax, effusion in the pleural space bilaterally, an increased diameter of the heart vessels and finally ground glass appearance in both lungs are indicative of acute HF (46). In a retrospective study by Jain et al the role of Quantitative CT (QCT) in HFpEF patients was explored. An algorithm of artificial intelligence (AI) was utilised in order to quantify the amount of fluid in the pulmonary system. This study showed that QCT enabled investigators to identify congestion of the pulmonary system in HFpEF patients who did not have related symptoms. Some of the advantages of using AI algorithm is that standard computers can run this application in a relatively small amount of time and that there is not any variability regarding the interpretation of the findings as no humans are involved. Nevertheless, further investigation is required to validate this technique (47).

2.4 Cardiac Magnetic Resonance

Cardiac Magnetic Resonance (CMR) is the gold standard modality for estimation of the volume of heart chambers and hence of EF. It can assist physicians in finding the cause of HF, in guiding treatment plans and in accurately assessing the structural and functional characteristics of the heart. Some of the factors limiting its use is the high cost and reduced availability, the poor quality of image if the patient has an arrythmia and the fact that CMR might not be compatible with some devices implanted on the patient (39, 48). According to a study conducted by Verma et al, the density of water in the lungs could be accurately estimated via CMR and is irrespectively related with increased mortality risk and hospitalizations associated with HF in HFrEF patients (49). Cheriyan et al concluded in an article published in PubMed in 2022 that Dynamic Contrast Enhanced MRI (DCE- MRI) could be employed as a method of estimation of fluid level in the interstitial space of the lungs in symptomatic HF patients. The use of gadolinium in this case helps in determining whether the water is located inside or outside of the vessels and thus aiding in better quantification of the existing fluid (50).

CHAPTER 3 - Biomarkers

3.1 Natriuretic Peptides

Biomarkers are undeniably a valuable tool when assessing congestion since they contribute significantly to diagnosis, prognosis and monitoring of treatment response. NPs, with Atrial- type NP (ANP) and Brain- type NP (BNP) being the most commonly used, are hormones which are produced and then secreted in the circulation by cardiac muscle cells when the end-diastolic stress in the cardiac chambers increases. ANP is mainly produced by the atria while BNP by the ventricles. These biomarkers are initially produced as pre-prohormones, which transform into their active forms, BNP and ANP, after undergoing cleavage. Both have several functions, with the former acting against cardiac hypertrophy and fibrosis and the latter acting as a vasodilator, diuretic and aldosterone inhibitor. Additionally, their role is vital in hindering the sympathetic nervous system, RAAS and the arginine- vasopressin system (AVP) all of which are overactivated in HF.

The byproducts of BNP and ANP are the inactive NT-proBNP and the mid-regional MR-proANP respectively. The half-life of BNP and ANP is short compared to NT- proBNP and MR-proANP, therefore the clearance of the former is faster. As a result, in clinical practice the levels of NT- proBNP and MR-proANP are quantified since they provide a reflection on the amount of BNP and ANP in plasma (41, 51, 52). Due to the fact that the levels of BNP provide a better estimation of the load of the LV and are also considered more sensitive and specific than ANP, they are used as the main diagnostic tool in HF cases (53). The cut-off levels which indicate congestion in acute HF are BNP > 100pg/mL, NT- proBNP >300 pg/mL and MR-proANP > 120pg/mL (53, 54). It is worth mentioning that NP testing is considered quite sensitive. However, due to their moderate specificity, further diagnostic work- up is required in case of positive results. (17, 55).

The use of NPs is very important in clinical practice, since it is recommended in all patients who present with symptoms of acute HF in order to confirm or exclude the diagnosis due to their high negative predictive value (94%-97%). They are considered objective, reproducible and most often widely available biomarkers and all these factors contribute significantly to their common use (51). Moreover, NP levels represent a very useful tool for guiding decongestive therapy in HF as their levels drop with the appropriate treatment (53). Nonetheless, these biomarkers have also well-known limitations as their circulating levels are affected by several conditions. More specifically in patients with either chronic renal dysfunction, atrial fibrillation or heart pathology of ischemic origin NP levels tend to be higher, while in obese or HFpEF patients lower levels are observed (17, 56). According to Cardinale et al, the predictive power of NPs increases when positive LUS findings in the emergency setting are combined with increased levels of NPs (30). Overall, the levels of these biomarkers offer valuable information regarding the diagnosis, treatment and possible outcomes of patients with HF (57).

3.2 Carbohydrate Antigen 125

Carbohydrate Antigen 125 (Ca- 125) or Mucin 16 (MUC16) is another useful congestion biomarker in HF. This glycoprotein is mainly produced from cells of the mesothelium in the pericardium, pleura and the peritoneum. Throughout the years, this marker was mainly used as a tool for diagnosing and monitoring treatment response in ovarian cancer. However, according to recent surveys it can also be used in the estimation of fluid overload and congestion. Further research is required to understand its main action; however, it is thought to participate in several pathways such as responses of the immune system to different triggers. This glycoprotein increases in malignancies, especially in ovarian cancer, in benign conditions and in acute HF where it depicts the level of congestion. In cases of acute HF, a level of Ca- 125 lower than 23 U / mL can serve as a prognostic marker, identifying the patients with a low probability of short-term unfavourable outcomes (58, 59). In fact, as congestion and inflammation are closely linked, it is speculated that long- term congestion of the venous system might result in inflammation, leading to Ca-125 production.

Some of the main advantages of this new biomarker is that it is easily found in most laboratories, it has standardized measurement with a low expenditure as well. Overall, as Ca- 125 levels might also be elevated in a range of different diseases including neoplastic syndromes, the increased levels of this marker should be interpreted alongside the rest of the information collected such as signs and symptoms, echocardiographic measurements and NP levels (31, 60). In a meta-analysis conducted by Li *et al,* the findings suggested that elevated Ca- 125 levels correlated with symptomatology of acute HF, HF related hospitalizations and death from any cause. As it can be derived from the obtained results, this biomarker could aid in the identification of HF patients with severe congestion and also as a follow- up tool after an acute HF episode (61).

3.3 ST- 2

Soluble suppression of tumorigenesis (sST2) is a promising biomarker in HF. More specifically, there are two sST2 isoforms including the transmembrane (ST2 ligand or ST2L) and the soluble isoform which circulates in the blood (sST2) and its levels are used as prognostic markers in both acute and chronic HF. Extracellularly, ST2 ligand binds with interleukin- 33 (IL-33) and this connection activates a signalling pathway which minimizes hypertrophy, fibrosis, death of cardiac muscle cells and hampers inflammation. On the other hand, the soluble isoform, sST2, can also bind the circulating IL- 33 and therefore hinders the cardioprotective effects of IL-33 and ST2L connection (62-64).

In cases of acute HF, sST2 levels rise significantly as its secretion is stimulated by an increase in the mechanical stress of the heart muscle cells. As sST2 is also associated with processes of the immune system, crucial information regarding both fibrosis and remodelling could be obtained (63). An important advantage of the use of ST2 levels is that in contrast to natriuretic peptides the soluble form of ST2 is not affected by the weight, age or kidney function of an individual (65). Additionally, compared with NPs whose levels rise whenever stretching of the heart chambers occurs and hence indicate the presence of HF, sST2 increased levels illustrate HF complications and more specifically remodelling (66).

In a survey carried out by Dudek et al, sST2 was found to be an independent risk factor of mortality from any cause in HFrEF stable patients (63). According to Bayes- Genis et al in an article published in the American Heart Association Journals, findings suggested that in the sST2 production apart from the myocardium, the pulmonary system and the endothelium of blood vessels participated as well. Thus, sST2 levels may provide an overview of the volume and inflammation status of heart chambers, lungs and the vasculature system in HF although further research is required (67). Currently, there is a Class IIb recommendation regarding measuring sST2 in chronic HF patients in order to predict outcomes and categorize individuals regarding their risk level (64).

CHAPTER 4 – Other Ways of Estimating Congestion

4.1 Plasma Volume

The reabsorption of water and sodium in HF results in an increase of the volume of fluids both inside of the blood vessels as well as in the interstitial compartment (68). Plasma Volume (PV) refers to the blood volume located intravascularly. There are several formulae utilized in the calculation of PV, however one of the most commonly used is the Strauss Formulae which aids in estimating alterations in PV over a period of time:

$$\Delta ePVS = 100\ X\ \frac{Hb\ (before)}{Hb\ (after)}\ X\ \frac{1-Ht\ (after)}{1-Ht\ (before)} - 100.$$

The values of Hemoglobin (Hb) and Hematocrit (Ht) obtained when a patient was admitted due to acute HF and when the patient was discharged after a decompensation regimen are used to calculate the PV (4, 69). A variation of this equation which does not require the initial Hb and Ht values is the Duarte Formulae in which the estimated PV status ePVS= $\frac{100-Ht(\%)}{Hb\ (g/dl)}$. Thus, ePVS can be easily calculated from the Complete Blood Count (CBC) obtained from the patient without the need of prior measurements (4, 70).

Bilchick et al conducted a survey in a cohort of patients with acute decompensation of HF from the ESCAPE Trial and their findings suggested that hospitalized patients in whom PV is decreased while renal function is maintained through the given treatment had indeed the most favourable outcomes (69). Another article published in 2016 by Darawsha et al found out that haemoconcentration in cases of acute HF is a positive prognostic indicator, however further assessment of congestion with other modalities is also required (71). Huang et al investigated the usefulness of ePVS in the subcategory of HFpEF. This study concluded that the Strauss equation is a valuable tool in monitoring the volume status of patients and in regulating the optimal treatment and diet plans (72). Generally, PV calculated through the given equations portrays an easily obtained in a non- invasive manner, low- priced tool enabling the estimation of congestion multiple times throughout the hospitalization of HF patients (73). Additionally, haemoconcentration could be used as a marker of decongestion (74).

4.2 Renal Function Tests

Malfunction of the renal system is frequently observed in HF patients. This phenomenon could be attributed to several coexisting factors some of which are congestion and poor perfusion of the renal system, dehydration arising from decongestive therapy, side-effects of the administered medication, nephroangiosclerosis and finally the result of neuroendocrine stimulation (4, 75). A decline of kidney function could either indicate congestion or it could suggest sufficient decongestion of the patient (4). Except from dysfunction of the renal parenchyma, congestion of the venous system is considered the factor with the highest impact regarding the deterioration of kidney function in cases of HF (76). A proposed mechanism is that the elevated CVP causes an increase in the backpressure of the kidney vasculature thus limiting the flow of blood in the renal system (77). A high percentage of urea is retained from the kidneys similarly to water and sodium retention in contrast to creatinine which is not reabsorbed. Elevation of the levels of Urea in HF, apart from malfunction of the heart and renal system, could also be indicative of congestion. Blood Urea Nitrogen (BUN) is considered a better prognostic indicator in cases of acute HF compared to Creatinine levels or estimated GFR (18). Overall, the ratio of BUN over Creatinine (BUN/ Cr) is thought to be a useful marker of congestion related dysfunction of the kidneys (4).

4.3 Right Heart Catheterization

Lastly, catheterization of the right heart chambers (or pulmonary artery catheterization) is undeniably the gold standard in order to accurately determine the level of congestion and filling pressures of cardiac chambers in an invasive way (4, 79). Although it is considered a procedure with a low probability of adverse events, severe complications might occur, including the formation of thrombus in the deep venous system, injury of the carotid artery, or even a possible rupture of the heart chambers. Even though, valuable information could be gathered by the utilization of this procedure, both its invasive nature as well as the tremendous improvement of techniques which are not invasive have significantly limited the use of this method in recent years (80). In cases of advanced HF where an accurate estimation of the volume status of patients is warranted the right heart catheterization provides valuable information (81).

4.4 Thoracic Impedance

Impedance quantifies the resistance of an element to a passing current. This method of assessing congestion in HF is based on the fact that in contrast to the tissue of the thorax which is solid, fluids oppose less resistance to current. Due to this, those body areas consisting mainly of fluid, such as blood, have lower impedances than other areas made up solely of tissue. This knowledge could be employed to estimate the level of congestion in HF (88). According to multiple investigations, a decline in the value of thoracic impedance is associated with fewer hospitalizations. Several surveys are currently investigating the applications of this method in clinical practice (4, 18).

4.5 Telemedicine

4.5.1 Cardio Mems

Nowadays, implantable monitoring systems which enable physicians to track the fluid status and related changes of HF patients have emerged. As changes in the hemodynamic status of a patient and the progressive increase in congestion often precede by a notable amount of time the decompensation of chronic to acute HF, the ability to monitor these variations is of vast importance. In fact, a steady change in the pressures of the pulmonary system takes place for some time before the occurrence of acute HF. CardioMEMS (Abbott, Sylmar, California) is an implantable system designed to estimate the pressure of the pulmonary artery where it is placed, which pressure correlates with the filling pressures of the LV (82, 83). According to the recorded measurements, clinicians may modify the given treatment in order to maintain the Pulmonary artery pressure between 10- 25 mmHg which depicts an ideal volume status for these patients. This device was approved by the Food and Drug Administration (FDA) in 2014 and according to some surveys which were conducted afterwards, a notable decline in hospitalizations was observed (82).

4.5.2 Remote Dielectric Sensing System

Another similar system to monitor congestion, also FDA approved, is the Remote Dielectric Sensing System (ReDS System- Sensible Medical Innivations- Israel). This device is capable of measuring the content of fluid in the lung, via a non- invasive wearable manner (84, 85). This equipment is highly sensitive and specific with a high negative predictive value as well (86). In a survey carried out by Bensimhon et al, it was found that substantial decongestion of the patients occurred when the given treatment was guided by ReDS; however, without any alteration of the rehospitalizations of the participants. Different results were obtained from a metanalysis investigating how efficient ReDS System was in preventing HF rehospitalizations. More specifically this survey concluded that with the assistance of this device, the likelihood of

rehospitalization in the three months following an admission declined. Additionally, due to the invasive nature and hence safety issues related with Cardio Mems, ReDS is considered a safer approach to prevent future hospitalizations (87). Several other similar devices have been designed recently, however the high cost associated with their usage is not affordable for many HF patients.

CONCLUSION

Overall, earlier identification and quantification of congestion levels in HF patients could have averted several decompensation episodes, rehospitalizations and associated deaths. All of the aforementioned ways could be particularly useful in the estimation of the degree of congestion. Regarding the proposed methods, more emphasis should be given in performing a more detailed clinical examination instead of solely relying on the technological and scientific advances of this era. Imaging methods are among the most commonly used tools to assess congestion. CXR and ultrasound methods are routinely used, while CT and MRI, although they are particularly useful entities in determining patients' volume status, are less frequently ordered. Regarding biomarkers, NPs are most often tested and the rest of the emerging biomarkers seem very promising, however further validation is required before their widespread application. EPVS can be easily calculated multiple times for a patient even though this calculation is rarely employed in clinical practice. Renal Markers and Body Weight alterations are easy to perform examinations and provide valuable insights as well; whereas, Right Heart Catheterization is limited for advanced HF cases due to the potentially lethal complications associated with its invasive nature. Nonetheless, this modality provides the most accurate results.

Lastly, telemedicine is a tremendously promising entity in the field of HF and the prevention of decompensation of patients. Nevertheless, further investigations and research is required. Although several tests could be employed for determining the fluid status of patients there is still not a single test or a standardized algorithm to facilitate in this direction and this could be a goal for the medical community in the following years.

ABBREVIATIONS:

HF: Heart Failure

EF: Ejection Fraction

LV: Left Ventricle

LVEF: Left Ventricular Ejection Fraction

HFrEF: Heart Failure with reduced Ejection Fraction

HFpEF: Heart Failure with preserved Ejection Fraction

HFmrEF: Heart Failure with mildly reduced Ejection Fraction

HFimpEF: Heart Failure with improved Ejection Fraction

MAP: Mean Arterial Pressure

CO: Cardiac Output

TPR: Total Peripheral Resistance

SV: Stroke Volume

LVEDV: Left Ventricular End Diastolic Volume

LVEDP: Left Ventricular End Diastolic Pressure

RAAS: Renin Angiotensin- Aldosterone System

CI: Cardiothoracic Index

RV: Right Ventricle

PND: Paroxysmal Nocturnal Dyspnoea

JVP: Jugular Venous Pressure

PCWP: Pulmonary Capillary Wedge Pressure

BMI: Body Mass Index

H&P: History and Physical Examination

CXR: Chest X-Ray

CSI: Congestion Score Index

ePVS: estimated Plasma Volume Status

TTE: Transthoracic Echocardiography

TR: peak regurgitation velocity through the tricuspid valve

LA: Left Atrium

LUS: Lung Ultrasound

COPD: Chronic Obstructive Lung Disease

NYHA: New York Heart Association

NP: Natriuretic Peptides

CVP: Central Venous Pressure

eGFR: estimated Glomerular Filtration Rate

CT: Computed Tomography

QCT: Quantitative CT

AI: Artificial Intelligence

CMR: Cardiac Magnetic Resonance

DCE- MRI: Dynamic Contrast Enhanced MRI

ANP: Atrial type NP

BNP: Brain type NP

AVP: Arginine Vasopressin System

Ca- 125: Carbohydrate Antigen 125

MUC16: Mucin 16

sST2: Soluble suppression of tumorigenesis

ST2L: ST2 ligand

IL-33: Interleukin 33

PV: Plasma Volume

Hb: Haemoglobin

Ht: Haematocrit

CBC: Complete Blood Count

BUN: Blood Urea Nitrogen

ReDS: Remote Dielectric Sensing System

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