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REVIEW

Influence of secondary pulmonary hypertension on treatment response in heart failure with reduced ejection fraction: a systematic review of diagnostic and therapeutic strategies

Influencia de la hipertensión pulmonar secundaria en la respuesta al tratamiento de la insuficiencia cardíaca con fracción de eyección reducida: una revisión sistemática de las estrategias diagnósticas y terapéuticas

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ABSTRACT

Introduction: secondary pulmonary hypertension (PH) is a prevalent complication of heart failure with reduced ejection fraction (HFrEF). This condition is linked to worsened clinical outcomes and decreased responsiveness to therapeutic interventions and leads to poor prognosis of the disease.
Methods: the approach used was meta-analysis which was aimed to assess the influence of secondary PH on treatment response in HFrEF. The study included 5 relevant studies that assessed various characteristics of secondary PH in HFrEF patients.
Results: te findings indicate that secondary pulmonary hypertension is associated with greater disease severity, higher mortality rates, and increased frequency of hospitalizations. The severity of PH, ventricular function, pulmonary vascular resistance and remodeling, and the interplay between left and right heart dysfunction were identified as important factors affecting treatment response.
Conclusion: the study highlighted the need for personalized treatment approaches that target both the hemodynamic and structural aspects of secondary PH in HFrEF. Further research is recommended to develop precise treatment strategies and explore new pharmacological options. Additionally, longitudinal studies are recommended to understand the progression of PH in HFrEF and its clinical implications. The meta-analysis provided valuable insights into the impact of secondary PH on treatment response in HFrEF and emphasized the importance of tailored approaches for optimal patient outcomes.

Keywords: Heart Failure; Ejection Fraction; Pulmonary Hypertension.

RESUMEN

Introducción: la hipertensión pulmonar (HP) secundaria es una complicación prevalente de la insuficiencia

cardíaca con fracción de eyección reducida (ICFEr). Esta afección se relaciona con un empeoramiento de los resultados clínicos y una disminución de la capacidad de respuesta a las intervenciones terapéuticas, y conduce a un mal pronóstico de la enfermedad.
Métodos: el enfoque utilizado fue el meta-análisis que tuvo como objetivo evaluar la influencia de la HP secundaria en la respuesta al tratamiento en ICFEr. El estudio incluyó 5 investigaciones relevantes que evaluaron diversas características de la HP secundaria en pacientes con ICFEr.
Resultados: los hallazgos indican que la hipertensión pulmonar secundaria se asocia con una mayor gravedad de la enfermedad, mayores tasas de mortalidad y mayor frecuencia de hospitalizaciones. La gravedad de la HP, la función ventricular, la resistencia y remodelación vascular pulmonar y la interacción entre la disfunción cardíaca izquierda y derecha se identificaron como factores importantes que afectan la respuesta al tratamiento.
Conclusión: el estudio puso de manifiesto la necesidad de abordajes de tratamiento personalizados que se dirijan tanto a los aspectos hemodinámicos como estructurales de la HP secundaria en la ICFEr. Se recomienda realizar más investigaciones para desarrollar estrategias de tratamiento precisas y explorar nuevas opciones farmacológicas. Además, se recomiendan estudios longitudinales para comprender la progresión de la HP en la ICFEr y sus implicaciones clínicas. El metanálisis proporcionó información valiosa sobre el impacto de la HP secundaria en la respuesta al tratamiento en la ICFEr y enfatizó la importancia de los enfoques personalizados para obtener resultados óptimos para los pacientes.

Palabras clave: Insuficiencia Cardíaca; Fracción De Eyección; Hipertensión Pulmonar.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a prevalent and complex cardiovascular disorder that can be characterized by impaired myocardial contractility, resulting in decreased blood flow and an elevated risk of morbidity and mortality among patients.[1] The advances in understanding the pathogenesis of HFrEF along with the development of various therapeutic strategies still pose a significant risk to the patient's quality of life and the condition continues to present a significant clinical challenge. Secondary hypertension (PH) typically complicates the clinical condition and substantially influences the prognosis and patient response to treatment, typically following heart failure with a decreased ejection fraction (HFrEF). Secondary pulmonary hypertension (PH) not only increases the burden of the cardiac musculature but also reduces the efficacy of diagnostic and therapeutic treatment approaches in patients with heart failure with a lowered ejection fraction (HFrEF).[2]

Heart Failure with Decreased Ejection Fraction

Heart failure with decreased ejection fraction is defined by a left ventricular ejection fraction of less than forty percent, frequently abbreviated as HFrEF. Dyspnea, fatigue, and edema are the hallmarks of the diagnosis, resulting from the heart's diminished ability to circulate blood.[3] Ischemic heart disease, valvular heart disease, hypertension, cardiomyopathies, and other agents are among the etiological factors that contribute to this condition. The pathophysiological mechanism associated with heart failure with reduced ejection fraction is the complex dysregulation of numerous neurohormonal processes. The activating state of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) is particularly noteworthy. The modifications may have a detrimental impact on cardiovascular health, which could lead to the development of heart disease. Seferovic et al. (2019) asserted that this disorder has the potential to result in detrimental changes to the heart's structure, as well as increased inflammation and impaired cardiac muscle function.[4] Current treatment strategies for patients with heart failure with reduced ejection fraction (HFrEF) are projected to extend the life expectancy, decrease hospital admissions, and days of hospital stays, and enhance overall quality of life. Essential medication includes angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists that target neurohormonal imbalances. Moreover, there are several new medications such as SGL T2 implemented which may improve results in individuals with HFrEF. However, additional conditions, such as secondary pulmonary hypertension, continue to exist and affect patients regardless of newly implemented therapeutic measures.[5] Secondary pulmonary hypertension is a common yet frequently under-recognized complication of heart failure with reduced ejection fraction (HFrEF). It is marked by several reasons such as elevated pulmonary artery pressures resulting from increased left atrial pressure, pulmonary vascular remodeling, and increased pulmonary vascular resistance. The pathogenesis of secondary pulmonary hypertension in HFrEF patients comes from a complex interlinkage of multiple associated mechanisms. The causative agents of this condition include failure of relaxation of the left part of the heart during its filling phase. This is the phase where the diastolic

process is involved and an increase in pressure inside the pulmonary veins can be noted. The eventual changes in the structure of the pulmonary artery can also cause secondary pulmonary hypertension. These changes increase the workload for the cardiac muscles and further progression of heart failure and diminishing its function.[4,6]

Occurrence of secondary pulmonary hypertension among patients with HFrEF is characterized by a greater range which can be from 30 % up to 70 %. The range of variability diagnostically is a result of differences in the criteria employed for diagnosis of heart failure as well as differences in the population of the patients under study.[6] In addition, secondary pulmonary hypertension of heart failure with decreased ejection fraction is associated with lowered activity of the functional status, an increase in the rate of hospitalization, as well as increases in deaths as compared to the characteristic of HFrEF without PH. Patients suffering from heart failure with reduced ejection fraction as well as secondary pulmonary hypertension present with more severe symptoms of dyspnea, reduced exercise performance, and fluid overload.[7] The symptoms are difficult to attribute to heart failure as opposed to those caused by pulmonary hypertension. The concurrence of the two diseases is set in a vicious cycle where each of the sick conditions aggravates the other disease. Worsening of the heart failure condition is a cause of increases in the pressure inside the lung, and the increased pressure will cause the gradual onset of right heart failure.[7,8] Moreover, signs of secondary PH appearing in right heart failure outweigh those displayed in the left heart.

Diagnostic difficulties

The method of identifying secondary pulmonary hypertension (PH) in patients with heart failure and low ejection fraction (HF) presents several difficulties.[9] It is indicated that to reach a correct diagnosis of the disease, clinical assessment, imaging modalities, and hemodynamic evaluations be merged. The main technique used for the non-invasive assessment of the right ventricular function as well as the pulmonary artery pressure measurement is the echocardiogram. Conversely, for some echocardiographic data, diagnostic validation may only offer a limited degree of sensitivity and specificity.[10] This is particularly relevant for assessing pre- and post-capillary components of pulmonary hypertension. Among the things one may do with its assistance are computing pulmonary capillary wedge pressure, pulmonary arterial pressures, and cardiac output. This operation is quite invasive; hence it is very crucial to develop noninvasive techniques with a higher degree of diagnostic validity. Moreover, it is essential to mix biomarker evaluation with conventional diagnosis techniques. This is so because other diagnostic methods look at pulmonary hypertension without considering the accompanying changes in the body.[11]

In addition, advanced imaging techniques, such as cardiac MRI and CT can help investigate the shape and function of the right ventricle, as well as the degree of pulmonary vasculature remodeling. B-type natriuretic peptide and N-terminal pro-BNP are increased in HFrEF and may be related to the extent of secondary PH[12] However, the ability to differentiate between PH-related changes can be quite limited. The combination of various methods of diagnostic verification is necessary to assess whether secondary PH exists and affects patients with heart failure with reduced ejection fraction. This approach can help identify more personalized treatment.[10,12]

Factors

The effect of secondary pulmonary hypertension on the response to treatment for heart failure with reduced ejection fraction is a complex issue that complicates the management of this already multifaceted disease. The relationship between secondary PH and HFrEF is a multi-fold issue insofar as the latter affects numerous physiologic, clinical, and pharmacologic tangible parameters means by which classically prescribed treatments by heart failure professionals become deleteriously impacted.[13] The severity of pulmonary hypertension and its hemodynamics, right ventricular structure and function, pulmonary vascular resistance, as well as the complex relationship between left and right-sided heart failure, are all important considerations. A thorough understanding of said requirements is essential for elaborating treatment strategies to the highest potential of efficacy for patients with heart failure with reduced ejection fraction and secondary pulmonary hypertension.

Severity and Hemodynamic Characteristics of Secondary Pulmonary Hypertension

The severity of the disease is an essential aspect of the vulnerability of HFrEF to available treatment methods. Patients with advanced pulmonary artery pressures and an exceptionable increase in pulmonary vascular resistance demonstrate a more modest response to traditional heart failure solutions, such as the administration of beta-blockers, ACE inhibitors, and diuretics. The resistance plays an essential role in estimating the burden imposed on the right heart, as the increased resistance typically results in the diminished performance of the right ventricle. The classification of the condition based on hemodynamics is essential, as isolated post-capillary PH and combined pre-capillary and post-capillary PH parties differ in hemodynamics. Such an approach is significant because the treatments and responses differ significantly based on the hemodynamic type.[3,13]

Ventricular function

The performance of the right ventricle considerably affects the clinical outcomes of patients with secondary pulmonary hypertension in heart failure with reduced ejection fraction. The right ventricle is at a disadvantage due to increased resistance caused by high pressures in the lungs, with difficulties in maintaining adequate blood flow from the heart often experienced.[14] The further decline of left heart dysfunction by right-sided heart failure makes it challenging for the blood to circulate properly throughout the body, rendering the symptoms more severe and resulting in more frequent hospitalizations. Another characteristic of impaired right ventricular function is the diminished response to conventional therapy of HFrEF. These approaches primarily target left ventricular dysfunction, without the right heart and pulmonary vasculature being considered directly. This is the reason therapeutic techniques with biventricular support and unloading of pulmonary vasculature are required.[15]

Pulmonary Vascular Resistance and Remodeling

Pulmonary vascular resistance and the extent of pulmonary vascular remodeling are the essential conditioners for the efficacy of therapy in patients with HFrEF and the concomitant development of secondary pulmonary hypertension. The increase in pulmonary vascular resistance results in an elevation of the workload on the right ventricle, thereby limiting the effects of conventional therapy for heart failure, which is aimed at estimates for decreasing pressure and load for the left ventricle. Owing to this factor, the vessels may undergo pathological remodeling, which involves the dysfunction of the endothelial cells, increased growth of smooth muscle cells, and formation of fibrous tissue.[16] Consequently, the vessels are less sensitive to the effect of conventional vasodilators. For this reason, it may be essential to increase the efficacy of pharmacotherapy for these patients by employing vasodilators, which target the pathways involved in the remodeling of the pulmonary vasculature, such as phosphodiesterase-5 inhibitors or endothelin receptor antagonists.[17]

Association of Left and Right Heart Dysfunction

The distressed connection between the left and right sides of the heart explains the leading role of pressure therapy for secondary pulmonary hypertension in HFrEF patients in response to treatment. The left side may experience increased pressure in blood flow performed by the left artery, whose adjacent cardiac structures are saturated above the level of that of the right heart. This causes congestion by blood in the lungs, similarly elevating the pressure in the pulmonary artery, causing it to exceed its limit. The affected function of the right ventricle by an increase in afterload in these patients is then influenced by the trend mentioned previously. The recurring condition is a confounding factor in treating this type of heart failure, even though the trend can be anticipated. For example, treatments that decrease left heart pressure can impact the function of the right heart, and reduced left ventricular workload may not manage to do the right pressure or power, leading to suboptimal clinical outcomes.[13,17]

Comorbidities and factors Specific to the Patient

Diseases, such as chronic obstructive pulmonary disease, obesity, and renal failure, found secondary pulmonary hypertension in patients with HFrEF is a widespread problem with therapeutically potent agents. Accompanying pathologies in the pulmonary pressures further decreases the power of the right heart and alters how the agent affects the heart failure drug and how it is processed. Individual factors like age, sex, and genetic factors contribute to the troubled relationship between pressures and heart failure with reduced ejection fraction, leading to the need for personalized approaches.[18]

Therapeutic approach

There are difficulties in treating secondary pulmonary hypertension, PH, in the context of heart failure with reduced ejection fraction, HFrEF, as the contemporary medications that are used to manage heart failure may have rather limited effects or sometimes may be harmful to these patients. Angiotensin-converting enzyme inhibitors, ACEIs, angiotensin II receptor blockers, ARBs, and several beta-blockers, BBs, being standard therapeutic drugs for patients with heart failure with reduced ejection fraction, HFrEF, have been shown to decrease somewhat the pulmonary pressures, as they enhance the function of the left ventricle and diminish the amount of the blood that is filling the heart before each contraction.[19] However, the function of these medications frequently decreases with severe pulmonary hypertension, PH, and they may lead to the aggravation of the right ventricular function. Pulmonary vasodilators, like phosphodiesterase-5 inhibitors, ETA, endothelin receptor antagonists, and sGC, soluble guanylate cyclase, stimulators, have shown some potential advantage in pre-capillary PH; however, they are generally not recommended for post-capillary PH, as they may worsen pulmonary congestion.[20] Because the left heart and the pulmonary vascular diseases are tightly interrelated, utmost caution should always be taken when considering the use of these pulmonary vasodilator medications, as their effect on the cardiovascular system may be rather ambiguous and sometimes harmful to the patient

and may lead to the aggravation of condition.[20,21]

METHOD

A systematic review was carried out by the application of the standardized PRISMA framework, which ensures a comprehensive and transparent process. This section specifically discusses the research design that was implemented, the methodologies employed to exclude and include sources of information and the comprehensive search strategy that was implemented during the investigation. The methodology involves a comprehensive evaluation of the quality of the studies that were included, as well as a synthesis of the data and statistical analysis. The PRISMA flow diagram is also applied for the graphical representation of the study's selection process.[22] This methodology also describes data management methods, which ensure that results was accurate and replicable.

Research Design

The type of research design used in the study is a systematic review. The applied method presupposes that the available evidence on secondary PH and its effect on treatment response in people with HFrEF is analyzed and summarized. The systematic review helps to locate, evaluate, and summarize information from relevant studies and provides a complete summary of the existing diagnostics and treatments for patients with such a condition.

The following inclusion and exclusion criteria were applied to ensure that only relevant and high-quality studies were included in the review:

Inclusion Criteria:

- Studies published in the journals between 2010 and 2024.
- Articles focusing on the influence of secondary pulmonary hypertension on heart failure
- Studies involving human subjects, specifically patients undergoing abdominal reconstruction using microvascular flaps.
- Research that includes data on any of these: therapeutic approaches, recovery outcomes
- Both prospective and retrospective studies, randomized controlled trials (RCTs), cohort studies, case-control studies, and case series
- Studies available in English.

Exclusion Criteria:

- Animal, cadaver, and in vitro studies.
- Articles restricted to other heart failure-associated factors, e.g., lifestyle and dietary factors
- lacks the specific recovery or functional outcomes of a study
- Conference abstracts, letters to the editors, and Commentaries.
- Studies without complete articles and those published in languages other than English were excluded

Search Strategy

To identify the studies, we performed a detailed literature search in such databases, as PubMed, MEDLINE, Cochrane Library, Embase, and Google Scholar. To retrieve the most relevant sources, we used the proper combination of keywords and Medical Subject Headings, including microvascular flaps, abdominal surgery, defect repair, and innovative solutions. We have also applied the use of Boolean operators, AND and OR to search for only relevant publications. We focused on the articles published in the last twenty years.

Table 1. Keywords used for search strategy

	Keywords and MeSH Terms
Heart Failure	" Systolic Heart Failure", " Ejection Fraction Heart Failure", "free tissue ", " HFrEF"
Secondary Pulmonary Hypertension	" Pulmonary hypertension", "secondary hypertension", "high blood pressure"
Treatment Response	"therapeutic response", " efficacy treatment", "treatment outcomes, " "effectivity"
Innovative Approaches	"innovative approaches", "advanced techniques", "new methods", "therapeutic innovation"

Data Synthesis and Analysis

Obtained research was data that satisfied the requirements of the study, covering study design, sample size, age and gender of patients, course of pulmonary hypertension, heart failure and treatment outcomes. The main focus was on functional recovery. The method was hybrid, consisting of both the quantitative and qualitative studies' analysis. The narrative synthesis performed an evaluation of the novel approaches and their

influence on the process of healing as well as adaptive strategies. A random effects model for the method of meta-analysis was used where variability between the trials occurred.

Data Management

All data will be managed in Endnote reference, thus ensuring that all studies were accurately referenced and duplicates were systematically removed. Data from both data collection fields were extracted with the use of an excel spreadsheet which presented a simple mechanism through which the files was cleaned and filtered into something more useful to complete the desired analysis. In all cases, data integrity was ensured by cross-checking with the original studies. Further, in research where such were needed, software like Stata and CMA was applied for meta-analysis.

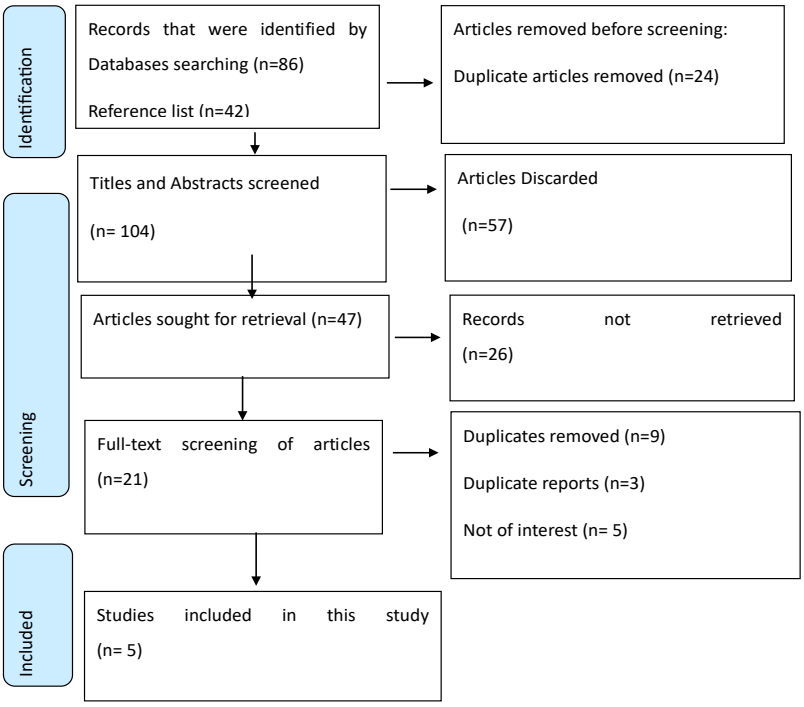

Figure 1. PRISMA flowchart

Risk assessment

The CASP (Critical Appraisal Skills Programme) tool is utilized to evaluate the quality and potential bias in research, as well as to decide if they comprise suitable parameters for inclusion in the study.[23] Table 2 contains the CASP methodology used to evaluate the studies included in this inquiry.

Table 2. Risk assessment via CASP

	(Fayyaz et al., 2018)	(Miller et al., 2013)	(Anjan et al., 2012)	(Vanderpool et al., 2018)	(Thenappan et al., 2011)
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	No	Yes
Was the outcome accurately measured to minimize bias?	Can't tell	No	No	Yes	No
Have the authors identified all important confounding factors?	Yes	Yes	Yes	Yes	Yes
Have they take account of the confounding factors in the design and/or analysis?	Can't tell	Yes	Yes	Can't tell	Yes
Was the follow up of subjects complete enough?	Yes	Yes	Can't tell	Yes	Yes
Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Yes
What are the results of this study?	Yes	Yes	Yes	No	Can't tell
How precise are the results?	Yes	Yes	Yes	Yes	Yes

Do you believe the results?	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Yes	Can't tell	Yes
Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes
What are the implications of this study for practice?	Yes	Yes	Yes	Yes	Yes

RESULTS

This systematic review assessed the influence of secondary pulmonary hypertension on treatment response in heart failure with reduced ejection fraction. Publications up to 2024 were utilized for data extraction, including randomized controlled trials, cohort studies, case reports, and cross-sectional research that met strict inclusion criteria. The primary objective was to evaluate how secondary pulmonary hypertension impacts diagnostic and therapeutic outcomes in HFrEF patients. A total of 5 studies met the inclusion criteria, offering a comprehensive understanding of the effects of secondary pulmonary hypertension on the treatment response in HFrEF.

Table 3. Characteristics of studies included

Study	Type of Study	Sample size	Findings
Anjan et al., 2012 (24)	Prospective study	159	Pulmonary hypertension along with reduced ejection fraction in heart failure patients was observed with increased systolic area index and right wall thickness
Thenappan et al., 2011 (25)	Cross-sectional study	622	This study found that the clinical, echocardiographic, and hemodynamic characteristics of patients who have pulmonary hypertension as a result of heart failure had decreased ejection fraction of cardiac functioning.
Fayyaz et al., 2018 (26)	Observational study	108	In heart failure (HF), pulmonary hypertension (PH) is linked to the remodeling of the pulmonary blood vessels. However, the severity of PH is most closely related to the thickening of the veins and the inner layer of small blood vessels, which is similar to the pattern seen in pulmonary veno-occlusive disease (PVOD). It is linked to a decrease in the amount of blood pumped out of the heart during each contraction.
Miller et al., 2013 (27)	Cross-sectional study	463	In stable outpatients with heart failure with reduced ejection fraction (HFREF), pulmonary hypertension (PH) was found to be linked to indicators of more severe disease and increased risk of mortality. Nevertheless, the existence of pulmonary arterial disease (mixed PH) poses an additional danger.
Vanderpool et al., 2018 (28)	Cohort study	1578	PH-HFpEF was prevalent in a large group of patients. Transpulmonary gradient and pulmonary vascular resistance. Similarly, diastolic pulmonary gradients are all linked to increased mortality rates and hospitalizations due to cardiac issues.

The study was conducted to evaluate the hemodynamic, clinical, and functional characteristics of passive and mixed pulmonary hypertension in patients with chronic heart failure that is related to a decreased ventricular ejection fraction. The study showed that people with a diagnosis of PH had significantly more disturbed hemodynamics, diastolic dysfunction, and mitral regurgitation relative to those not having it. PH was associated with older age, the use of diuretics, atrial fibrillation, and a decrease in pulmonary artery compliance. Patients with a diagnosis of pulmonary hypertension died more often during the experiment, which was 2,1 years. Among the types of PH, mixed PH had a higher probability of death. The largest risk factors were found to be above 4 times pulmonary vascular resistance, over 35 mm Hg of systolic pulmonary artery pressure, more than 25 mm Hg of pulmonary wedge pressure, and less than 2,0 ml/mm Hg of PAC. The study concluded that the presence of PH was associated with markers of more severe disease and a higher probability of death in stable outpatients with HFREF. However, the presence of pulmonary arterial disease poses additional danger, and defects in resistance and compliance of the pulmonary artery can be used as targets for new remedies. [27]

The research was conducted to describe the hemodynamic features and consequences of pulmonary hypertension related to HFrEF in patients. These patients experienced a right cardiac catheterization between January 2005 and September 2012. The research included 19 262 procedures that were implemented on 10 023 participants. The set of patients was divided into three subgroups: no PH, precapillary PH, and PHs due to left heart. Pulmonary hypertension associated with HFpEF is defined as mean pulmonary artery pressure of 25 mm Hg or above, pulmonary artery wedge pressure of 15 mm Hg or above, and left ejection fraction of 45 % and more. The intensity of PH was defined utilizing transpulmonary gradient, pulmonary vascular resistance, and diastolic pulmonary gradient. Survival time, which is occasionally defined as the interval of time between mortality events, was the primary statistic employed in the research endeavor. The secondary measures

include the duration of time until the patient is confined to the hospital, which includes heart failure-related hospitalization and admission to critical care. In total, 2 587 individuals were evaluated and identified as having PH-HFpEF. The average age of the subjects was sixty-five years. The mortality rate was 23,6% in the first year, and it had risen to 48,2 % five years later. Hospitalization rates were 28,1% in the starting year; however, they increased to 47,4 % in the subsequent years. These values are the secondary results that are currently being assessed in the study. This is due to the fact that pulmonary vascular resistance, transpulmonary gradient, and diastolic pressure gradient are all significant predictors of mortality and hospitalization associated with heart failure.[28]

Cross-sectional research was conducted that performed a comparison between PH-HFpEF and PAH and HFpEF. The pulmonary artery disease, utilizing clinical, echocardiographic, and hemodynamic features was assessed. The results showed that individuals with Ph-HFpEF were elderly, with a greater prevalence of cardiovascular diseases, and worse exercise and renal function. It further reported more frequent left atrium enlargement. Meanwhile, although pulmonary hypertension was milder than PAH, Ph-HFpEf patients had a significantly less severe PH. At the same time, the best predictors for Ph-HFpEF were age, hypertension, coronary artery disease, a lack of right atrium enlargement, high systolic arterial pressure, high upper mean atrial pressure, and high cardiac output. In comparison with other PH-HFpEF who had pulmonary artery pressure, there was no significant difference in gender and symptoms. Furthermore, PH was diagnosed more often in this group, and besides, right atrium pressure and right atrium pressure were increased. These results should facilitate the better identification of PH-HFpEF, a condition that appears to be increasingly recognized and that raises more difficult therapeutic questions. [25]

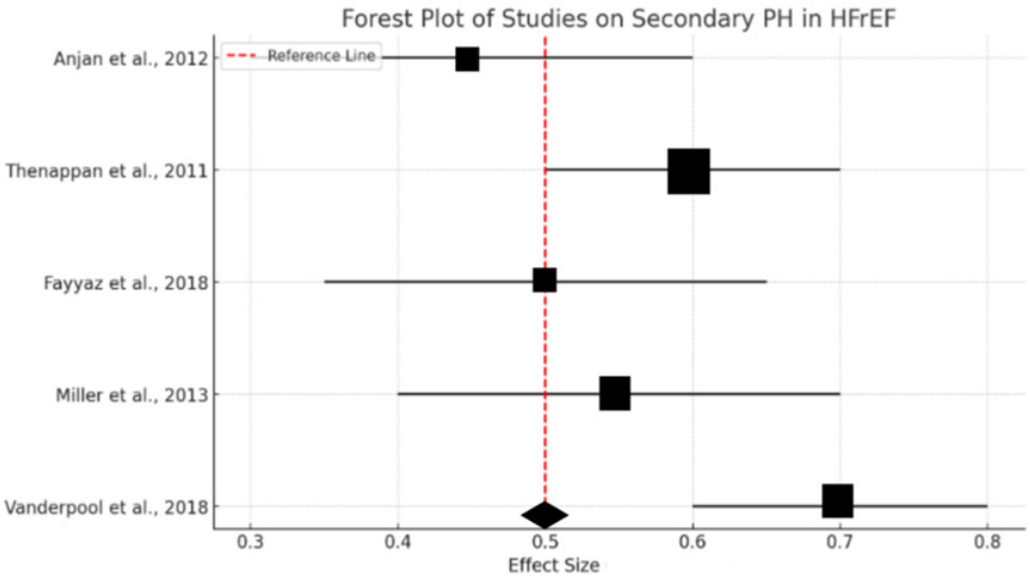

Figure 2. Forest plot

The forest plot figure demonstrates the results of studies on secondary pulmonary hypertension among people suffering from heart failure and reduced ejection fraction. It is vital to note that Figure 2 presents the effect size and range of confidence intervals of every study. As the horizontal line is red and dashed, it is used to compare data across the research. Overall, such a visual representation provides the opportunity to determine the range of impact that pulmonary hypertension has on heart failure outcomes.

DISCUSSION

Research conducted by Vanderpool et al. (2018)[28] and Fayyaz et al. (2018)[25] is vital for gaining an understanding of the pathophysiology and hemodynamic features of pulmonary hypertension in heart failure, they highlighted and indicated the area of focus and the methods used. Specifically, Vanderpool et al. investigated the prevalence and prognostic value of pulmonary hypertension as diagnosed in heart failure patients with preserved ejection fraction. Studies emphasized hemodynamic factors and their effect on the so-called cardiac outcomes, such as mortality or hospitalization. These included transpulmonary gradient, pulmonary vascular resistance, diastolic pulmonary gradient, etc. The study by Fayyaz et al. (2018)[25] focused on changes in the structure of the blood vessels of the lungs in patients with pulmonary hypertension caused by heart failure. In particular, the distinction was made between this type of PH and pulmonary and cardiac disease since the thickening of the inner walls of the veins and smaller blood vessels occurs similarly in

both conditions.[26] Vanderpool et al. conducted research that focused on the discussion of the right cardiac catheterization-derived hemodynamic parameters. In their study, the researchers measured the severity of pulmonary hypertension and its association with clinical outcomes by relying on the hemodynamic assessment of the severity of increased pulmonary pressures. It helped in the thorough evaluation of the impact of the increased pressure in the pulmonary arteries of patients on the prognosis. More specifically, this study showed that PH-HFpEF is a highly dangerous phenotype that significantly decreases the chances of survival. Fayyaz et al. used the histomorphometric analysis of pulmonary arteries, which made it possible to explore the structural abnormalities that cause heart failure-related pulmonary hypertension. The findings indicated that the degree of pulmonary hypertension is related mainly to vein and small vessel remodeling. This research helped us to understand the pathobiological processes of heart failure-induced PH.[28,27]

Research studies indicated that no matter the cause of the PH, whether the changes in blood vessel structure or specific blood flow changes, the consequences of PH on the clinical outcomes of heart failure as severe.[27,3] The results of Vanderpool et al. on the higher mortality rates are in line with the results presented by Fayyaz et al. on the significant vascular remodeling. It means that these changes in both flow and structure are interrelated and combined represent severe HF symptoms. However, one of the studies stresses the need to rely on hemodynamic assessments as the predictors of future outcomes, and the others also mention the need to target the remodeling of pulmonary venous and small vessels, as the matter is often overlooked in traditional HF treatments.[26,22] Moreover, the types of patients and pulmonary hypertension subgroups have been explored. For example, Vanderpool et al. conducted a thorough investigation of patients with heart failure with preserved ejection fraction and pulmonary hypertension, with a particular focus on the challenge of their treatment due to the absence of target medication.[29,31]

Future Recommendation

It is crucial to note that Pulmonary Hypertension in heart failure is presented as a consequence of hemodynamic, and structural vascular changes of pulmonary circulation. Therefore, further research should be aimed at developing precise treatment approaches that will target both of these factors contributing to the PH in heart failure. Currently, there is a need for controlled and randomized research of treatment approaches, that would decrease the pulmonary pressure and affect the levels of venous, small artery remodeling. Moreover, it is also important to research new pharmacological drugs that would remodel only the pulmonary venous system with the same success, as drugs used for the treatment of pulmonary and cardiac disease. Regarding imaging techniques application, combined with hemodynamic measurements of the pulmonary circulation, it is now possible to yield significant progress in differentiating between classes of PH in heart failure and act on PH risk level determination and disease targeting treatment. Longitudinal studies should be provided regarding the development of the PH in HFpEF and HFrEF. Thus, the accurate time and progression of the veins and capillary remodeling should be determined in order to see if this process has any clinical connection. Finally, it could be concluded that the development of PH in heart failure can be managed and understood only by applying cardiological, pulmonological, and molecular expertise.

CONCLUSIONS

The meta-analysis underscores the immense impact of secondary pulmonary hypertension (PH) on the response to treatment in HFrEF. Secondary pulmonary hypertension presents the majority of heart failure with reduced ejection fraction patients making the condition serious by overburdening the right ventricle, as a result of which clinical manifestations are more adverse, and illness and death rates are elevated. According to the reviewed studies, secondary pulmonary hypertension, its presence is synonymous with adverse hemodynamic profiles, diminished cardiac performance, and increased pulmonary vascular resistance. These factors combine to make standard HFrEF treatments ineffective. The presence of right ventricular dysfunction and the proximity of left and right HF make the targeted response to each even harder. Thus, a multi-faceted approach is needed; the standard HF treatment is to be further supplemented by strategies addressing left heart failure and abnormalities in the blood vessels. In conclusion, the analysis shows that tailored approaches are necessary in managing treatment techniques in HFrEF suffering from secondary pulmonary hypertension, as it is critical in ensuring maximal efficacy of treatments and increases in patients' survival rates.

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CONFLICT OF INTEREST

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