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Advances in the Detection of Hepatopulmonary Syndrome in Cirrhotic Patients: A Comprehensive Review

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ABSTRACT

***Background*:** Hepatopulmonary syndrome (HPS) is a clinically important vascular complication of chronic liver disease, most frequently encountered in cirrhotic patients. It is defined by the presence of chronic liver disease, arterial oxygenation abnormalities, and evidence of intrapulmonary vascular dilatations. Although historically underdiagnosed, HPS has been increasingly recognized over the past two decades as a distinct syndrome that adversely impacts prognosis and quality of life in cirrhotic patients. Reported prevalence varies widely, ranging from 10% to 30% among patients with advanced liver disease, largely due to variability in diagnostic approaches and heterogeneity of studied populations. The syndrome carries prognostic significance since its presence is independently associated with reduced survival and increased post-liver transplantation complications. Early detection of HPS remains a clinical challenge due to the subtle and non-specific nature of its respiratory manifestations, which are often masked by underlying hepatic symptoms or concurrent cardiopulmonary disease. Conventional diagnostic tools such as arterial blood gas analysis and pulse oximetry provide important screening value, while contrast-enhanced echocardiography and lung perfusion scans remain the gold standard methods for confirming intrapulmonary shunting. Recent advances in imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine approaches, have added to the diagnostic armamentarium, although their use in routine practice remains limited. Parallel to imaging, research into circulating biomarkers and experimental diagnostic assays offers promise for earlier and non-invasive detection. The aim of this review is to provide a comprehensive overview of the detection strategies for hepatopulmonary syndrome in cirrhotic patients, highlighting established clinical tools, novel imaging approaches, and emerging biomarkers. The review also emphasizes the prognostic implications of HPS detection, challenges in differentiating it from other hypoxemic conditions, and future perspectives in refining diagnostic algorithms. By integrating advances across clinical, imaging, and laboratory domains, this article aims to guide clinicians toward earlier recognition and improved patient outcomes in hepatopulmonary syndrome associated with cirrhosis.

Keywords: Hepatopulmonary Syndrome, Cirrhotic Patients

INTRODUCTION

Hepatopulmonary syndrome (HPS) represents a clinically relevant intersection between hepatic and pulmonary pathology, where chronic liver disease leads to pulmonary vascular abnormalities that impair oxygenation. It is characterized by the triad of chronic liver disease, abnormal arterial oxygenation, and evidence of intrapulmonary vascular dilatations. Unlike hepatic hydrothorax or portopulmonary hypertension, which are more easily recognized, HPS is often overlooked due to its nonspecific clinical manifestations such as dyspnea, platypnea, or orthodeoxia [1]. The true burden of disease is likely underestimated, with prevalence studies reporting that 10–30% of patients with cirrhosis may develop HPS depending on diagnostic criteria and patient population [2].

The detection of HPS carries significant clinical importance. Patients with HPS exhibit reduced quality of life, higher morbidity, and poorer survival compared with cirrhotic patients without the syndrome. Importantly, liver transplantation remains the only curative option, and early identification of HPS significantly influences transplant eligibility and outcomes [3]. Hence, diagnostic accuracy is central not only to patient prognostication but also to guiding timely referral for liver transplantation evaluation.

Despite its clinical importance, several diagnostic challenges persist. The spectrum of HPS ranges from mild, asymptomatic oxygen desaturation to severe hypoxemia that dominates the clinical presentation. Standard screening with pulse oximetry is widely accessible but may lack sensitivity in detecting early disease. Arterial blood gas analysis is a cornerstone test, yet not routinely applied in all cirrhotic patients. Gold standard methods, such as contrast-enhanced echocardiography and lung perfusion scintigraphy, remain underutilized outside of specialized centers [4]. Consequently, a gap persists between recommended diagnostic practices and real-world application, leading to underrecognition of the syndrome.

Recent advances in diagnostic modalities have expanded the spectrum of tools available for HPS detection. These include novel imaging approaches such as computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scans capable of quantifying intrapulmonary shunting with greater accuracy. Additionally, experimental use of circulating biomarkers, exhaled breath tests, and dynamic physiologic assessment tools are being investigated to improve diagnostic precision [5]. Despite these promising advances, their integration into routine clinical care is limited, and a clear consensus on optimal screening strategies remains lacking.

This review article aims to critically evaluate advances in the detection of HPS among cirrhotic patients. It synthesizes conventional diagnostic tools, novel imaging modalities, and experimental approaches while highlighting prognostic implications, diagnostic limitations, and future research directions. Ultimately, the goal is to provide a framework that guides clinicians toward early, accurate, and clinically impactful recognition of HPS in cirrhotic populations. [6]

Epidemiology and Clinical Significance of HPS in Cirrhosis

The epidemiology of hepatopulmonary syndrome (HPS) has been explored across multiple populations, revealing prevalence estimates that vary significantly depending on diagnostic methodology, geographic setting, and patient characteristics. Studies consistently report that between 10% and 30% of patients with cirrhosis develop HPS, with higher rates observed in individuals with advanced liver disease and portal hypertension [7]. This variation is attributable to heterogeneity in screening strategies, with some studies relying solely on pulse oximetry while others incorporate contrast-enhanced echocardiography or perfusion scanning [8]. Importantly, HPS may occur in any stage of cirrhosis, although the risk appears to increase with worsening hepatic dysfunction, alcohol-related liver disease, and viral hepatitis [9].

The clinical significance of HPS extends beyond the pulmonary manifestations. Multiple cohort studies have demonstrated that the presence of HPS in cirrhosis independently predicts worse overall survival compared with cirrhotic patients without the syndrome [10]. The natural history of HPS is characterized by progressive arterial hypoxemia, which significantly contributes to morbidity and compromises exercise tolerance, daily functioning, and overall quality of life. Unlike portopulmonary hypertension, which contraindicates liver transplantation, HPS is considered an indication for transplant, as reversal of hypoxemia frequently occurs after successful graft implantation [11]. Thus, accurate epidemiologic understanding is vital for timely identification and referral to transplant programs.

Regional studies highlight important differences in prevalence and presentation. In Western populations, HPS is most commonly reported in alcohol-related cirrhosis and hepatitis C, while in Asian countries, hepatitis B–related cirrhosis predominates as the underlying cause [12]. Furthermore, environmental and genetic factors may contribute to the variability in prevalence rates.

Notably, certain polymorphisms related to nitric oxide signaling pathways have been linked to increased susceptibility to HPS, suggesting a role for host genetic predisposition [13]. This geographic and genetic heterogeneity underscores the importance of standardized diagnostic protocols in epidemiologic research.

The underdiagnosis of HPS has critical implications for patient outcomes. Given that many cirrhotic patients undergo transplant evaluation, failure to detect HPS may result in inappropriate risk stratification and perioperative complications. Conversely, timely diagnosis allows for prioritization on transplant waiting lists, as several countries incorporate HPS severity into allocation systems [14]. Therefore, accurate epidemiologic data and widespread awareness among hepatologists and pulmonologists are crucial to ensure equitable care.

In summary, HPS is a relatively common but underrecognized complication of cirrhosis with significant clinical implications. Its epidemiology is shaped by methodological, geographic, and genetic factors, and its presence carries prognostic weight that directly influences management decisions and transplantation outcomes [15].

Pathophysiology of Hepatopulmonary Syndrome

The pathophysiology of hepatopulmonary syndrome (HPS) is complex and multifactorial, involving an interplay between chronic liver disease, portal hypertension, and pulmonary vascular alterations. The defining feature is intrapulmonary vascular dilatation (IPVD), which leads to abnormal gas exchange and hypoxemia [16]. These vascular changes include both dilation of precapillary arterioles and the development of direct arteriovenous communications, resulting in increased alveolar–capillary distance and impaired oxygen diffusion. The degree of hypoxemia correlates with the extent of IPVDs rather than the severity of underlying liver dysfunction, highlighting the independent contribution of pulmonary vascular pathology [17].

Nitric oxide (NO) overproduction plays a central role in the development of IPVD. Studies have demonstrated increased pulmonary endothelial nitric oxide synthase (eNOS) expression in cirrhotic patients with HPS, leading to excessive vasodilation and impaired hypoxic pulmonary vasoconstriction [18]. In animal models of biliary cirrhosis, blocking NO production reduces the extent of IPVDs and improves arterial oxygenation, underscoring its pathogenic significance. Beyond NO, other vasodilators such as carbon monoxide and prostacyclin have been implicated in perpetuating pulmonary vascular dilation [19].

Inflammation is another key driver in HPS pathogenesis. Bacterial translocation and endotoxemia, common in cirrhotic patients, contribute to pulmonary macrophage activation. These macrophages release cytokines such as tumor necrosis factor-α (TNF-α), which further induce NO production and vascular remodeling [20]. In experimental models, gut decontamination with antibiotics reduces pulmonary intravascular macrophage accumulation and ameliorates hypoxemia, highlighting the gut–lung–liver axis in HPS development [21].

Angiogenesis and vascular remodeling also contribute to the pathophysiology. Increased expression of vascular endothelial growth factor (VEGF) has been observed in the lungs of patients with HPS, promoting abnormal vascular proliferation and shunt formation [22]. This dysregulated angiogenesis explains the persistence of intrapulmonary shunting even in the absence of overt vasodilation. Importantly, these vascular changes are often diffuse and heterogeneously distributed, which complicates imaging and detection strategies.

The interplay of these mechanisms culminates in ventilation–perfusion mismatch, diffusion–perfusion limitation, and direct right-to-left intrapulmonary shunting, all contributing to hypoxemia. Clinically, this manifests as platypnea (worsening dyspnea in the upright position) and orthodeoxia (desaturation when upright), both of which reflect gravity-dependent increases in perfusion of dilated vessels in the lung bases [23]. Recognizing these unique physiologic features is critical in guiding diagnostic strategies, as they distinguish HPS from other pulmonary complications of cirrhosis.

In summary, HPS arises from a cascade of pathophysiological processes involving vasodilation, inflammation, angiogenesis, and altered vascular remodeling. These mechanisms disrupt pulmonary gas exchange and highlight potential therapeutic targets, though detection remains the essential first step in management [24].

Clinical Manifestations and Natural History

The clinical manifestations of hepatopulmonary syndrome (HPS) are often subtle and easily overlooked in cirrhotic patients, as respiratory symptoms may be overshadowed by hepatic dysfunction. The hallmark clinical features include dyspnea, platypnea, and orthodeoxia. Dyspnea, the most frequent symptom, may occur at rest or with exertion and is often progressive over time

[25]. Platypnea refers to worsening dyspnea in the upright position, while orthodeoxia describes oxygen desaturation when moving from supine to upright posture. These unique positional phenomena are considered highly suggestive of HPS and relate to the gravity-dependent increase in perfusion of dilated vessels within the lung bases [26].

Physical examination findings in HPS are often nonspecific, but may include cyanosis and digital clubbing in more advanced cases. Telangiectasias and vascular spiders are frequently observed, reflecting systemic vascular dysregulation associated with cirrhosis [27]. In patients with severe hypoxemia, arterial oxygen saturation may fall dramatically with minimal exertion, leading to exercise intolerance and significant impairment in daily activities. Unlike portopulmonary hypertension, which manifests with exertional dyspnea and right heart failure signs, HPS tends to present with hypoxemia out of proportion to pulmonary or cardiac symptoms [28].

The natural history of HPS is progressive, with arterial oxygenation declining over time in many patients. Longitudinal studies suggest that mild cases may remain stable for months, while moderate-to-severe cases demonstrate worsening hypoxemia and functional limitation [29]. Importantly, the progression of HPS is not directly correlated with the severity of underlying liver disease, meaning that patients with compensated cirrhosis may still present with clinically significant HPS [30]. This disconnect complicates detection, as reliance on hepatic disease stage alone is insufficient to identify at-risk individuals.

HPS has a significant impact on survival independent of liver disease severity. Several cohort studies have confirmed that cirrhotic patients with HPS have reduced survival compared with matched cirrhotic controls, even after adjusting for Model for End-stage Liver Disease (MELD) scores [31]. The presence of severe hypoxemia is associated with increased mortality both before and after liver transplantation. Post-transplant outcomes, although generally favorable in terms of hypoxemia reversal, remain variable, with some patients experiencing prolonged recovery of oxygenation [32].

Overall, the clinical manifestations of HPS are distinctive yet underrecognized, and its natural history is marked by progressive hypoxemia with adverse prognostic implications. Recognition of these features is crucial for timely diagnosis and referral to transplantation programs, emphasizing the importance of systematic screening in cirrhotic populations [33].

Conventional Diagnostic Approaches

Arterial Blood Gas (ABG) Analysis

Arterial blood gas analysis remains one of the cornerstones in the diagnosis of hepatopulmonary syndrome (HPS). The key diagnostic hallmark is an increased alveolar–arterial (A–a) oxygen gradient, often accompanied by hypoxemia [34]. In cirrhotic patients, an A–a gradient >15 mmHg (or >20 mmHg in those older than 64 years) is considered abnormal and highly suggestive of HPS in the appropriate clinical setting. The degree of hypoxemia can be further classified as mild, moderate, or severe, which aids in both clinical decision-making and liver transplantation prioritization [35]. However, ABG measurement is invasive, and its use as a screening tool is limited in routine practice. Despite these challenges, it remains essential for definitive assessment, particularly in patients with borderline oxygen saturation or atypical presentations [36].

Pulse Oximetry

Pulse oximetry offers a non-invasive, readily available screening method for HPS detection. It is particularly useful in outpatient settings and liver transplantation evaluations. A resting oxygen saturation below 96% is often considered abnormal, warranting further confirmatory testing [37]. The advantage of pulse oximetry lies in its simplicity and accessibility, though it has lower sensitivity compared with ABG in detecting mild hypoxemia. Studies suggest that the test is most effective in identifying moderate-to-severe HPS, whereas early or subclinical cases may be missed [38]. Nevertheless, pulse oximetry is recommended as an initial screening modality for cirrhotic patients, especially given its ability to detect orthodeoxia in the upright position [39].

Contrast-Enhanced Echocardiography

Contrast-enhanced transthoracic echocardiography (CE-TTE) is considered the gold standard diagnostic tool for detecting intrapulmonary vascular dilatations in HPS. The technique involves injection of agitated saline microbubbles, which normally do not pass through the pulmonary capillary bed. In patients with HPS, delayed appearance of microbubbles in the left atrium (typically after 3–6 cardiac cycles) indicates intrapulmonary shunting [40]. CE-TTE is highly sensitive, widely available, and safe, making it the preferred confirmatory test for HPS detection. It also allows differentiation from intracardiac shunts, which

produce earlier bubble transit [41]. Despite its strengths, CE-TTE requires expertise in interpretation and may not quantify the severity of shunting, limiting its use for longitudinal monitoring [42].

Lung Perfusion Scanning

Lung perfusion scintigraphy using technetium-99m–labeled macroaggregated albumin (99mTc-MAA) provides a quantitative method for assessing intrapulmonary shunting. After intravenous injection, the tracer should normally be trapped in the pulmonary circulation. In HPS, however, shunted particles bypass the pulmonary capillary bed and localize in extrapulmonary organs such as the brain or kidneys, with uptake >6% considered diagnostic [43]. Lung perfusion scanning complements CE-TTE by offering a semiquantitative assessment of shunt magnitude, though it is less sensitive in detecting small IPVDs [44]. The test is often reserved for patients in whom echocardiography is inconclusive or contraindicated, and it is also useful in research settings where quantification of shunt severity is needed [45].

Collectively, conventional diagnostic approaches—ABG, pulse oximetry, CE-TTE, and perfusion scanning—form the foundation for detecting HPS in cirrhotic patients. While each modality has strengths and limitations, their combined use provides a comprehensive evaluation of gas exchange abnormalities and intrapulmonary shunting, ensuring accurate diagnosis and guiding management [46].

Role of Advanced Imaging in HPS Detection

Computed Tomography (CT) Imaging

Computed tomography (CT) has increasingly been investigated as a tool to identify pulmonary vascular abnormalities in hepatopulmonary syndrome (HPS). High-resolution CT (HRCT) may reveal subtle pulmonary changes such as increased vascular caliber in the lower lobes and enhanced visibility of peripheral pulmonary vessels extending to the pleural surface [47]. These findings are consistent with intrapulmonary vascular dilatations (IPVDs), although they lack specificity and may be missed in early disease. Contrast-enhanced CT has also been utilized to detect abnormal vascular enhancement patterns, but its role remains supplementary to echocardiography rather than diagnostic in isolation [48]. Despite its limitations, CT is particularly valuable when coexistent pulmonary pathology, such as chronic obstructive pulmonary disease or interstitial lung disease, complicates the diagnostic picture [49].

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) provides functional and structural information in HPS, particularly through contrast-enhanced and perfusion-based sequences. Studies have demonstrated that MRI can quantify pulmonary blood flow distribution abnormalities and detect intrapulmonary shunts with high sensitivity [50]. Unlike CT, MRI avoids radiation exposure and offers superior soft tissue contrast, making it an appealing non-invasive option for repeated assessments. However, availability, cost, and the need for advanced expertise limit its routine use. Recent experimental approaches, such as hyperpolarized gas MRI, show promise for evaluating regional ventilation–perfusion mismatch in HPS with greater precision [51].

Nuclear Medicine and Functional Imaging

Nuclear medicine techniques, beyond the conventional technetium-99m macroaggregated albumin (99mTc-MAA) perfusion scan, are being studied for their potential to improve diagnostic accuracy. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) can provide three-dimensional visualization of shunt distribution, offering more detailed assessment of intrapulmonary vascular alterations [52]. Furthermore, the integration of SPECT with CT (SPECT-CT) allows for both functional and anatomical evaluation, which may enhance the detection of subtle shunts that elude planar imaging. These modalities, however, remain primarily research tools and are not yet standardized in clinical practice [53].

Emerging Imaging Approaches

More advanced imaging techniques, including dual-energy CT and functional MRI, are being explored as novel methods for assessing pulmonary oxygenation and vascular dynamics in HPS. Dual-energy CT enables assessment of regional lung perfusion by mapping iodine distribution, potentially identifying perfusion abnormalities related to intrapulmonary shunting [54]. Similarly, oxygen-enhanced MRI can non-invasively assess lung oxygenation at a regional level, offering unique insights into the physiological consequences of IPVDs. While these methods remain experimental, they hold promise for future clinical integration, particularly in transplant evaluation where accurate disease staging is critical [55].

In conclusion, advanced imaging modalities provide valuable adjunctive information in the detection of HPS. While CT and MRI contribute to structural and functional assessment, nuclear imaging and emerging technologies offer greater precision in quantifying shunts and perfusion abnormalities. At present, these techniques complement but do not replace conventional tools such as echocardiography and perfusion scanning. Their future role will likely expand as evidence accumulates and technology becomes more accessible [56].

Biomarkers and Experimental Diagnostic Methods

Circulating Biomarkers

The search for reliable circulating biomarkers in hepatopulmonary syndrome (HPS) has gained momentum, given the limitations of conventional imaging and physiologic tests. Nitric oxide (NO) metabolites, such as plasma nitrate and nitrite levels, have been proposed as potential markers due to the well-established role of NO overproduction in the pathogenesis of intrapulmonary vascular dilatations [57]. Elevated levels of endothelin-1 and carbon monoxide–related markers have also been documented, reflecting systemic vascular dysregulation in cirrhotic patients with HPS [58]. While these biomarkers demonstrate correlation with disease severity, their diagnostic specificity is limited, as similar abnormalities may be observed in other forms of cirrhosis-related vasodilation.

Inflammatory Mediators

Cytokines and inflammatory mediators have emerged as another group of potential diagnostic biomarkers. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are consistently elevated in cirrhotic patients with HPS compared with those without the syndrome, supporting the role of systemic inflammation and bacterial translocation in HPS development [59]. Similarly, soluble adhesion molecules and markers of macrophage activation have been investigated for their diagnostic potential, although most studies remain preliminary. Their role appears promising for risk stratification but requires further validation in larger, multicenter cohorts [60].

Exhaled Breath Analysis

Exhaled breath testing has been explored as a non-invasive diagnostic tool. Elevated levels of exhaled nitric oxide (eNO) have been reported in HPS patients, consistent with enhanced pulmonary NO production [61]. Unlike circulating NO metabolites, eNO directly reflects pulmonary endothelial activity, making it more specific to the pulmonary component of HPS. Similarly, breath condensate analysis has identified oxidative stress markers that correlate with hypoxemia severity. Although not widely available, these approaches may serve as convenient bedside tests in the future [62].

Genomic and Proteomic Approaches

Recent advances in molecular biology have prompted investigation into genomic and proteomic markers in HPS. Genetic polymorphisms affecting NO synthase, endothelin, and vascular endothelial growth factor (VEGF) pathways have been linked to increased susceptibility to HPS in cirrhotic populations [63]. Proteomic studies have identified unique plasma protein signatures in affected patients, some of which relate to angiogenesis and vascular remodeling. These findings suggest that molecular profiling may eventually enable personalized detection and risk stratification [64].

Experimental Imaging-Biomarker Integration

A growing field of research focuses on integrating biomarker discovery with advanced imaging modalities. For instance, PET imaging using radiolabeled tracers targeting inflammatory or angiogenic pathways has shown potential for detecting intrapulmonary shunting at an earlier stage [65]. Such approaches could bridge the gap between structural imaging and biochemical abnormalities, enhancing diagnostic accuracy. However, their use remains confined to research settings at present.

In conclusion, while conventional methods remain central to HPS detection, biomarkers and experimental diagnostics represent a promising frontier. NO-related metabolites, inflammatory cytokines, exhaled breath markers, and molecular signatures provide insights into disease pathophysiology and may complement traditional diagnostic tools. Larger studies and standardization are required before their integration into clinical practice, but their potential to improve early detection is substantial [66].

Screening and Diagnostic Algorithms in Cirrhotic Patients

Importance of Screening

Given the prognostic implications of hepatopulmonary syndrome (HPS), systematic screening in cirrhotic populations is crucial, particularly in patients undergoing liver transplantation evaluation. Studies indicate that many patients with HPS remain undiagnosed until advanced disease develops, underscoring the need for early and structured detection strategies [67]. The aim of screening is to identify patients with subclinical hypoxemia or intrapulmonary vascular dilatations (IPVDs) before overt symptoms emerge, allowing timely referral for transplantation work-up and management [68].

Initial Screening Tools

The first step in screening typically involves non-invasive tools such as pulse oximetry, given its ease of use and widespread availability. A resting oxygen saturation (SpO_2) <96% in cirrhotic patients is considered abnormal and should prompt further testing with arterial blood gas (ABG) analysis [69]. Upright and supine SpO_2 measurements are particularly helpful for detecting orthodeoxia, a classic feature of HPS. Patients with abnormal findings should undergo confirmatory testing, most often with contrast-enhanced transthoracic echocardiography (CE-TTE) [70].

Diagnostic Confirmation

CE-TTE remains the diagnostic gold standard for confirming IPVDs in suspected cases. Its ability to differentiate intrapulmonary from intracardiac shunts makes it indispensable in the diagnostic algorithm [71]. In cases where echocardiography is inconclusive or unavailable, lung perfusion scintigraphy using technetium-99m macroaggregated albumin (99mTc-MAA) provides an alternative method to demonstrate and quantify extrapulmonary shunting [72]. ABG analysis remains a necessary adjunct to establish the presence and severity of hypoxemia, which is critical for staging the syndrome and prioritizing transplant allocation.

Algorithmic Approach

An evidence-based diagnostic algorithm has been proposed:

1. **Initial screening** with pulse oximetry in all cirrhotic patients, especially those being evaluated for liver transplantation.
2. **Abnormal SpO_2 (<96%)** → perform ABG to confirm hypoxemia and calculate A–a gradient.
3. **Confirmatory testing** with CE-TTE to identify intrapulmonary shunting.
4. **Additional testing** with 99mTc-MAA lung perfusion scan in uncertain cases or for quantification of shunt fraction [73]. This stepwise approach ensures both sensitivity and specificity while minimizing unnecessary invasive testing.

Integration into Transplant Evaluation

Current guidelines recommend mandatory HPS screening in all patients undergoing transplant assessment. The diagnosis not only influences prognosis but also impacts liver allocation systems, as HPS is recognized as a Model for End-Stage Liver Disease (MELD) exception condition in many countries [74]. Integration of systematic screening into pre-transplant work-ups has improved detection rates, but adherence remains variable across centers, indicating the need for standardized protocols [75].

In summary, effective screening and diagnostic algorithms for HPS rely on a combination of pulse oximetry, ABG, CE-TTE, and, when needed, perfusion scintigraphy. Structured implementation in cirrhotic populations, particularly transplant candidates, is essential for timely detection and improved outcomes [76].

Prognostic Value of HPS Detection

The detection of hepatopulmonary syndrome (HPS) in cirrhotic patients carries significant prognostic implications that extend beyond the presence of chronic liver disease alone. Multiple studies have demonstrated that HPS is independently associated with increased mortality, irrespective of the severity of hepatic dysfunction measured by conventional scores such as the Child–Pugh classification or the Model for End-Stage Liver Disease (MELD) score [77]. This underscores the importance of routine detection, as HPS contributes uniquely to adverse outcomes in cirrhotic patients.

One of the most critical prognostic features of HPS is the degree of hypoxemia. Patients with moderate-to-severe arterial oxygenation impairment exhibit substantially reduced survival compared with those with mild disease [78]. Severe hypoxemia (PaO_2 <50 mmHg) is associated with particularly poor outcomes, including higher pre-transplant mortality and increased risk of perioperative complications. Importantly, this hypoxemia progresses independently of hepatic disease severity, suggesting that pulmonary vascular changes evolve along a distinct trajectory that must be addressed in patient care [79].

The detection of HPS also directly influences transplant prioritization. In many countries, including those under the United Network for Organ Sharing (UNOS), patients with HPS are eligible for MELD exception points, which grant increased priority on transplant waiting lists [80]. This policy reflects recognition of the adverse prognosis associated with HPS and the potential for liver transplantation to reverse pulmonary abnormalities. However, the prognostic benefit is not uniform; patients with severe hypoxemia often have longer recovery times after transplantation and higher rates of early post-operative complications, although long-term survival may approximate that of non-HPS recipients [81].

Several studies have confirmed that successful liver transplantation reverses hypoxemia in the majority of HPS patients, often within 6–12 months [82]. Nevertheless, delayed or incomplete resolution is observed in a subset of patients, particularly those with severe disease at baseline. This highlights the need for early detection, as timely transplantation is associated with better outcomes and faster reversal of pulmonary abnormalities. Moreover, detection prior to transplantation allows clinicians to anticipate perioperative risks and optimize patient management [83].

In addition to transplant outcomes, the prognostic significance of HPS extends to quality of life. Patients with untreated HPS suffer greater exercise intolerance, increased healthcare utilization, and reduced functional capacity compared with cirrhotic patients without HPS [84]. Thus, early identification is not only critical for survival but also for optimizing patient well-being.

In summary, the detection of HPS provides essential prognostic information, guiding both clinical management and transplant allocation. The degree of hypoxemia remains the strongest predictor of outcome, reinforcing the importance of structured screening and timely referral for transplantation [85].

Challenges in Diagnosis and Limitations of Current Methods

Nonspecific Clinical Presentation

One of the greatest challenges in diagnosing hepatopulmonary syndrome (HPS) is its nonspecific and often subtle clinical presentation. Symptoms such as dyspnea, fatigue, and exercise intolerance are common in cirrhotic patients and may be attributed to anemia, ascites, muscle wasting, or concomitant cardiopulmonary conditions [86]. Consequently, HPS frequently remains undiagnosed until advanced hypoxemia develops. Platypnea and orthodeoxia, although relatively specific, are not universally present, which further complicates early clinical recognition [87].

Overlap with Other Pulmonary Conditions

The differential diagnosis of hypoxemia in cirrhotic patients is broad, including chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary embolism, and portopulmonary hypertension. Distinguishing HPS from these conditions is critical, as management strategies differ significantly. For example, hypoxemia in COPD results from airway obstruction and ventilation–perfusion mismatch, whereas in HPS it is due to intrapulmonary vascular dilatations [88]. The presence of coexistent pulmonary disease can obscure diagnostic findings, particularly in imaging, making accurate detection challenging [89].

Limitations of Conventional Tests

Although arterial blood gas (ABG) analysis and pulse oximetry are essential tools, they lack sensitivity for early disease. Mild HPS may present with normal oxygen saturation at rest, with abnormalities only unmasked during exertion or positional testing [90]. Contrast-enhanced echocardiography, the gold standard, is highly sensitive but requires expertise for accurate interpretation and may not be universally available. Furthermore, CE-TTE does not provide quantitative assessment of shunt severity, limiting its utility in monitoring disease progression [91]. Lung perfusion scintigraphy, while capable of quantifying shunt fraction, suffers from relatively low sensitivity for small intrapulmonary shunts and involves radiation exposure [92].

Variability in Diagnostic Protocols

Another limitation lies in the lack of standardized diagnostic protocols across institutions. Studies reveal significant variability in screening practices, with some centers relying primarily on pulse oximetry, while others implement routine ABG and echocardiography [93]. This inconsistency leads to heterogeneous prevalence estimates and underdiagnosis in clinical practice. Moreover, there is no global consensus on the best approach to screen asymptomatic cirrhotic patients, leaving clinicians uncertain about whom to test and when [94].

Underutilization in Transplant Evaluation

Despite its prognostic significance, HPS remains underdiagnosed in transplant candidates. Surveys indicate that not all transplant centers routinely screen for HPS, even though it confers Model for End-Stage Liver Disease (MELD) exception points in many regions [95]. Failure to detect the syndrome in this setting results in missed opportunities for earlier prioritization and optimization of perioperative care. This highlights a critical gap between guideline recommendations and real-world practice.

In conclusion, the diagnosis of HPS is hindered by nonspecific symptoms, overlap with other pulmonary conditions, and limitations of current diagnostic modalities. Variability in protocols and underutilization in transplantation evaluation further contribute to underrecognition. Addressing these challenges requires standardized algorithms, broader access to diagnostic modalities, and increased clinician awareness [96].

Conclusion

Hepatopulmonary syndrome (HPS) remains a significant yet underrecognized complication of cirrhosis, with important implications for patient survival, transplant prioritization, and quality of life. Despite advances in understanding its pathophysiology and clinical manifestations, early detection continues to be a major challenge due to nonspecific symptoms, overlap with other cardiopulmonary disorders, and limitations of conventional diagnostic tools.

Traditional approaches such as arterial blood gas analysis, pulse oximetry, contrast-enhanced echocardiography, and lung perfusion scintigraphy remain the cornerstone of diagnosis. However, they are often underutilized or inconsistently applied, leading to variability in detection rates. Recent progress in advanced imaging techniques, biomarker discovery, and non-invasive physiologic assessments has provided promising avenues for improving diagnostic accuracy, though most remain investigational.

Screening algorithms that integrate non-invasive tools with confirmatory imaging are critical, particularly for patients being evaluated for liver transplantation, where timely recognition directly influences eligibility and outcomes. The prognostic value of HPS detection lies not only in guiding transplant prioritization but also in anticipating perioperative risks and monitoring recovery after transplantation. Importantly, patients diagnosed and transplanted earlier tend to achieve more rapid and complete reversal of hypoxemia compared with those identified at advanced stages.

Looking forward, greater standardization in diagnostic protocols, broader access to advanced imaging, and validation of biomarker-based approaches will be essential for integrating new strategies into clinical practice. Increased awareness among hepatologists, pulmonologists, and transplant teams will also be necessary to close the gap between guideline recommendations and real-world implementation.

In conclusion, advances in the detection of HPS offer significant opportunities to improve patient care. By combining established diagnostic methods with emerging technologies and structured screening algorithms, clinicians can ensure earlier recognition, better prognostication, and ultimately improved outcomes for cirrhotic patients affected by this complex syndrome.

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