Original Article

Evaluation of the Impact of an Echocardiographic Diagnosis of Pulmonary Hypertension on Patient Outcomes

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ABSTRACT

Background: Although detection of elevated right ventricular systolic pressure (RVSP) on routine echocardiography is common, its clinical significance is underappreciated. The recent change in the hemodynamic definition of pulmonary hypertension (PH) lowering the threshold from mean pulmonary arterial pressure ≥ 25 mm Hg to > 20 mm Hg further clouds the picture.

Methods: A retrospective cohort study was performed on residents of the South East Local Health Integration Network (population 495,000), Ontario, Canada, who underwent transthoracic echocardiography at

RÉSUMÉ

Contexte : Bien qu'une pression systolique ventriculaire droite (PSVD) élevée soit fréquemment mise en évidence au cours d'une échocardiographie systématique, sa portée clinique s'avère sous-estimée. La modification récente de la définition hémodynamique de l'hypertension pulmonaire (HP), faisant passer le seuil de la pression artérielle pulmonaire moyenne de ≥ 25 mmHg à > 20 mmHg, embrouille davantage la situation.

Méthodologie : Une étude rétrospective a été réalisée au sein d'une cohorte de résidents du territoire du Réseau local d'intégration des

Pulmonary hypertension (PH) is defined as a sustained resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg assessed by right heart catheterization (RHC).^{1,2} In 2019, the Sixth World Symposium on Pulmonary Hypertension updated this definition to mPAP > 20 mm Hg.³ Although RHC is the gold standard for diagnosis of PH, evidence of PH is often first suspected with Doppler echocardiography showing an elevated right ventricular systolic pressure (RVSP). A meta-analysis of 29 studies shows that the correlation between RVSP derived from echocardiography and systolic pulmonary arterial pressure from RHC is 0.70 (0.67 to 0.73), which suggests echocardiography is a reliable investigation to screen for the presence of PH.⁴ An RVSP ≥ 40 mm Hg is considered elevated.^{5–11} Given the new hemodynamic definition of PH, we hypothesize that RVSP from echocardiography is also going to be low. We investigate the clinical relevance of RVSP

between 30 and 40 mm Hg, which corresponds to an mPAP of 20 to 25 mm Hg calculated using a validated formula: $mPAP = 0.61 \times RVSP + 2$ mm Hg.¹²

RVSP is not the only echocardiographic parameter that reflects right ventricular (RV) function. Other parameters, such as elevated right atrial (RA) volume index,¹³ increased RV dimension,¹⁴ reduced tricuspid annular plane systolic excursion (TAPSE),¹ and decreased TAPSE to RVSP ratio,¹⁵ have been shown to independently predict poor RV function. In this study, we examine the relationship and correlation between RVSP and other RV structural and functional echocardiographic parameters.

In clinical practice, elevated RVSP is commonly encountered on echocardiography. A recent study by an Australian group found 18.7% of patients had elevated RVSP > 40 mm Hg in the National Echocardiography Database of Australia.¹⁶ Given the recent change in PH definition, the prevalence of patients with borderline elevation of RVSP between 30 and 40 mm Hg is understudied. However, by lowering the diagnostic threshold, we expect further increase in the prevalence PH.

PH is a complex disease with diverse etiologies. To facilitate clinical categorization, the World Health Organization (WHO) divides PH into 5 groups based on clinical history.¹⁷ Group 1 PH or pulmonary arterial hypertension (PAH) includes syndromes in which the primary pathology is in the

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Ethics Statement: This study was approved by the Health Sciences Research Ethics Board at Queen's University and Kingston Health Sciences Centre (KHSC).

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the Kingston Health Sciences Centre between February 19, 2013, and December 31, 2016. The index echocardiography from 9291 unique patients was obtained.

Results: A total of 2049 patients (22.1%) had an RVSP ≥ 40 mm Hg, 2040 patients (22.0%) had an RVSP ≥ 30 and < 40 mm Hg, but only 284 patients (3.1%) had a clinical diagnosis of PH. Although patients with an RVSP ≥ 40 mm Hg had the highest Charlson Comorbidity Index (CCI) (1.81 ± 0.05) and number of hospitalizations 1 year before the echocardiography (1.24 ± 0.03), patients with RVSP between 30 and 40 mm Hg also had significantly higher CCI (1.19 ± 0.04) and hospitalization (0.87 ± 0.03) compared with the CCI (0.84 ± 0.03) and hospitalization (0.65 ± 0.02) of patients with RVSP < 30 mm Hg ($P < 0.0001$).

Conclusion: Despite the finding that an elevated RVSP ≥ 30 mm Hg is common and predicts adverse outcomes, most patients with elevated RVSP are not reported as having PH or investigated. The significance of the elevated RVSP is underappreciated.

pulmonary vasculature (eg, idiopathic PAH, heritable PAH, and PH associated with 2 infectious diseases [human immunodeficiency virus and schistosomiasis], drugs, and connective tissue diseases).¹ Group 2 PH is associated with left heart diseases.¹ Group 3 PH is related to lung diseases or hypoxia.¹ Group 4 PH is associated with chronic thromboembolic disease.¹ Group 5 PH is a collection of PH syndromes due to unclear multifactorial mechanisms.¹

On the basis of the definition of mPAP ≥ 25 mm Hg, a recent study by our group showed that the incidence and prevalence of groups 1 to 4 PH, based on International Classification of Diseases 10th Revision (ICD-10) codes for comorbidities of PH, are increasing in Ontario, Canada.¹⁸ More importantly, a diagnosis of any group of PH, regardless of the presumptive WHO Group, was associated with a 7.2-fold increase in the 1-year standardized mortality ratio.¹⁸ Given the change in PH definition, what about patients with moderately elevated RVSP between 30 and 40 mm Hg? We hypothesize that patients with RVSP between 30 and 40 mm Hg, which was previously considered normal, also have significantly higher comorbidities and worse clinical outcomes compared with patients with RVSP less than 30 mm Hg.

We undertook a single-centre, retrospective cohort study to (1) identify the prevalence of elevated RVSP ≥ 40 mm Hg and RVSP ≥ 30 and < 40 mm Hg on echocardiography, noting the prevalence of patients who had a clinical diagnosis of PH by an ICD-10 code; (2) report the structural and functional changes in the right heart that correlate with Doppler detection of elevated RVSP; and (3) examine the relationship between elevated RVSP and patient comorbidities and outcomes.

Methods

This study follows Strengthening the Reporting of Observational Studies in Epidemiology recommendations for reporting cohort studies.¹⁹ The study was approved by the

services de santé du Sud-Est (population de 495 000 personnes) de l'Ontario (Canada) ayant subi une échocardiographie transthoracique au Centre des sciences de la santé de Kingston entre le 19 février 2013 et le 31 décembre 2016. L'échocardiographie de référence de 9 291 patients différents a été obtenue.

Résultats : La PSVD était ≥ 40 mmHg chez 2 049 patients (22,1 %) et ≥ 30 et < 40 mmHg chez 2 040 patients (22,0 %), mais un diagnostic clinique d'HP n'avait été posé que chez 284 patients (3,1 %). L'indice de comorbidité de Charlson (ICC) le plus élevé ($1,81 \pm 0,05$) et le plus grand nombre d'hospitalisations un an avant l'échocardiographie ($1,24 \pm 0,03$) ont été notés chez les patients qui présentaient une PSVD ≥ 40 mmHg; néanmoins, les valeurs de ces paramètres se sont aussi révélées significativement plus élevées chez les patients affichant une PSVD allant de 30 à 40 mmHg (ICC : $1,19 \pm 0,04$; hospitalisations : $0,87 \pm 0,03$) comparativement aux patients présentant une PSVD < 30 mmHg (ICC : $0,84 \pm 0,03$; hospitalisations : $0,65 \pm 0,02$) ($p < 0,0001$).

Conclusion : Malgré le fait qu'une PSVD élevée (≥ 30 mmHg) soit d'observation courante et prédictive de résultats cliniques défavorables, la plupart des cas ne sont pas signalés en tant que manifestation d'HP et ne font l'objet d'aucune investigation. La portée d'une PSVD élevée s'avère sous-estimée.

Health Sciences Research Ethics Board at Queen's University and Kingston Health Sciences Centre (KHSC).

Echocardiography

All echocardiograms were obtained by experienced cardiac sonographers using GE VIVID E9 (General Electric Company, Chicago, IL) and Philips EPIQ 7 and IE33 (Philips Healthcare, Markham, ON, Canada) cardiac ultrasound machines. Images were stored digitally using commercial software (Philips Healthcare, Markham, ON, Canada) and reported by board certified echo-cardiologists in accordance with published guidelines.

Standard complete 2-dimensional echocardiography was performed in all individuals, with chamber quantification assessed according to published criteria.²⁰ Pulmonary arterial pressure was assessed in all patients by imaging the peak velocity of the tricuspid regurgitant jet, using the simplified Bernoulli equation: $RVSP = 4v^2 + RA$ pressure. Values for RA pressure were estimated from measures of inferior vena cava (IVC) diameter: IVC ≤ 2.1 cm that collapses $> 50\%$ with a sniff = RA pressure of 3 mm Hg was assigned, whereas an IVC diameter > 2.1 cm that collapses $< 50\%$ with a sniff = RA pressure of 15 mm Hg.²¹ In scenarios in which IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mm Hg was used.²¹ Because this study included consecutive echocardiographic studies, from a clinical ultrasound laboratory, the sample also captured results from those patients who had no detectable tricuspid regurgitation jet or in whom the jet was inadequate to allow detection of a diagnostic quality Doppler interrogation. This latter group is heterogenous and includes both patients with normal hearts and patients with technically difficult images.

Data collection

Echocardiogram results between February 19, 2013, and December 30, 2016, were extracted from the KHSC Philips

Figure 1. Study design flowchart. Data were obtained from 11,360 echocardiography reports of 9291 patients between February 19, 2013, and December 30, 2016, from the Kingston Health Sciences Centre (KHSC). Only the index echocardiography report from each patient was included. Patients were divided into 4 groups based on right ventricular systolic pressure (RVSP). These groups were (1) no RVSP, (2) RVSP < 30 mm Hg, (3) RVSP 30 to 40 mm Hg, and (4) RVSP ≥ 40 mm Hg.

Xcelera cardiology information management system. For patients who had more than 1 echocardiogram performed during this time period, the first available was chosen as the index echocardiogram (Fig. 1). Only the index echocardiogram for each unique patient was included in the study.

Diagnostic codes (ICD-10) for conditions that could be risk factors for PH were identified (Supplemental Table S1). These codes were used to extract comorbidities for patients from the Kingston General Hospital Research Institute database, based on discharge abstraction and emergency visits. Any diagnoses made 2 years before and 2 years after the index echocardiography were captured. A binary scoring system was used; “1” meant the patient had at least 1 listed ICD-10 code that comprised a specific comorbid diagnosis, and “0” meant the patient had none of the listed ICD-10 codes for that specific diagnosis. In addition, comorbidities were grouped according to the WHO PH classification and used to determine the group/s to which a patient with an echocardiographic diagnosis of PH might belong to (Supplemental Table S2). This method was previously validated by our group.¹⁸ The Charlson Comorbidity Index (CCI) for each

patient was obtained from Kingston General Hospital Research Institute.^{22,23} The CCI is well validated for disease burden and the relative risk of death using clinical covariates.^{22,23} The number of hospital admissions 1 year before and 1 year after the index echocardiogram date were obtained to characterise the contact of patients with the healthcare system.

Data analysis

The collected data were analyzed using Microsoft Excel (Microsoft, Inc., Redmond, WA) and GraphPad Prism 8 (GraphPad Software, Inc., La Jolla, CA). The level of significance was set at $P < 0.05$. Statistical calculations were performed using GraphPad Prism 8 (GraphPad Software, Inc.).

Study outcomes

The cohort was divided into 4 groups: no RVSP, RVSP < 30 mm Hg, RVSP ≥ 30 and < 40 mm Hg, and RVSP ≥ 40 mm Hg (Fig. 1). Study population characteristics are displayed using pie charts and percentages in Figures 2 and 3. The frequency distribution of RVSP is displayed using histogram divided into 5 mm Hg intervals (Fig. 4). Echocardiography parameters are displayed using box whiskers plot (1-99 percentile) (Fig. 5), and corresponding data are displayed as mean ± standard deviation. Clinical data are displayed using histograms (Fig. 6), and corresponding data are displayed as mean ± 95% confidence interval, where appropriate. Finally, a subgroup analysis was performed on patients with RVSP > 30 and < 40 mm Hg dividing them into quartiles based on RVSP (Fig. 7). For multiple comparisons, a 1-way analysis of variance, followed by Tukey’s multiple comparisons test, was performed to evaluate echocardiographic parameters and clinical comorbidities.

Results

Study population characteristics

A total of 11,360 echocardiograms from 9291 unique patients were obtained. The cohort had a mean age of 66.0 ± 0.2 years, and 4280 (46.1%) were women. The cohort was divided into 4 groups: no RVSP (n = 3094, 33.3%),

Figure 2. Study population characteristics. (A) Twenty-two percent of patients had an RVSP ≥ 30 and < 40 mm Hg, and 22.1% of patients had an RVSP ≥ 40 mm Hg on echocardiography. RVSP measurement is most commonly due to insufficient tricuspid regurgitation. (B) Only 3.1% of patients had an International Classification of Diseases 10th Revision (ICD-10) diagnosis of pulmonary hypertension (PH). (C) Among patients with an ICD-10 diagnosis of PH, the percentage of patients in each PH group was determined by comorbidities associated with each group according to the World Health Organization PH classification. Supplemental Table S2 shows details.

Figure 3. Frequency distribution of RVSP in 6195 patients in whom RVSP could be estimated.

RVSP < 30 mm Hg ($n = 2106$, 22.7%), RVSP ≥ 30 and < 40 mm Hg ($n = 2040$, 22.0%), and RVSP ≥ 40 mm Hg ($n = 2049$, 22.1%) (Fig. 2A). The cohort was also assessed on the basis of the presence or absence of an ICD-10 clinical diagnosis of PH ($n = 284$, 3.1% vs $n = 9005$, 96.9%, respectively) (Fig. 2B). Among patients with the diagnosis of PH ($n = 284$), the most common form of comorbidities was group 2 comorbidities (21.8%), followed by group 3 comorbidities (7.4%), group 1 comorbidities (7.0%), and group 4 comorbidities (3.2%). Most patients had comorbidities that would qualify them for more than 1 PH group (60.8%) (Fig. 2C, Supplemental Table S2). Among the 6195 patients with a reported value for RVSP, the mean value was 37.36 ± 0.17 mm Hg. The frequency distribution of RVSP is shown in Figure 4. The distribution of RVSP was skewed toward the right, and the median RVSP for patients with and without the diagnosis of PH was 60.2 and 34.2 mm Hg, respectively.

Characteristics of patients' echocardiographic profiles

Patients with RVSP ≥ 40 mm Hg (74.3 ± 12.9 years) were significantly older than patients with RVSP between 30 and 40 mm Hg (69.9 ± 14.5 years), RVSP < 30 mm Hg (62.2 ± 17.2 year), and no RVSP (60.6 ± 16.0 years), $P < 0.0001$ (Fig. 5A). Left ventricular ejection fraction was reduced with increasing RVSP (Fig. 5B). Increased RVSP was associated with enlarged right ventricle and atrium. The mean RV diastolic dimension was 4.0 ± 0.7 cm for patients with RVSP ≥ 40 mm Hg, which was significantly higher compared with patients with RVSP between 30 and 40 mm Hg (3.7 ± 0.6 cm), RVSP < 30 mm Hg (3.6 ± 0.6 cm), and no RVSP (3.5 ± 0.6 cm) ($P < 0.0001$) (Fig. 5C). The RA-volume index for patients with RVSP ≥ 40 mm Hg (32.7 ± 18.0 mL/m²) was markedly higher than that of patients with RVSP between 30 and 40 mm Hg (24.6 ± 12.1 mL/m²), RVSP < 30 mm Hg (22.0 ± 9.9 mL/m²), and no RVSP (19.0 ± 7.6 mL/m²), $P < 0.0001$ (Fig. 5D). TAPSE was significantly reduced only in patients with RVSP ≥ 40 mm Hg (1.99 ± 0.54 cm), and there was no difference between patients with RVSP between 30 and 40 mm Hg (2.14 ± 0.49 cm), RVSP < 30 mm Hg (2.14 ± 0.46 cm), and no RVSP (2.17 ± 0.49) (Fig. 5E). The TAPSE to RVSP ratio was markedly lower in patients with RVSP ≥ 40 mm Hg (0.39 ± 0.14 mm Hg) compared with patients with RVSP between 30 and 40 mm Hg (0.62 ± 0.16 mm Hg), and RVSP < 30 mm Hg (0.88 ± 0.23 mm Hg).

Clinical characteristics and comorbidities of PH

The prevalence of an ICD-10 diagnosis of PH increased with increasing RVSP (11.66% in RVSP ≥ 40 mm Hg, 1.08% in RVSP 30 to 40 mm Hg, 0.24% in RVSP < 30 mm Hg, and only 0.58% in no RVSP, Fig. 6A). Likewise, more patients with higher RVSP had RHC: 4.93% patients with RVSP ≥ 40 mm Hg, 1.91% in patients with RVSP between 30 and 40 mm Hg, 0.85% in patients with RVSP < 30 mm Hg, and 0.87% in patients with no RVSP (Fig. 6B). The CCI increased with increasing RVSP, but the CCI was similar in patients with no RVSP and RVSP between 30 and 40 mm Hg (Fig. 6C). Patients with higher RVSP also had higher hospitalization both before and after the index echocardiography date: RVSP ≥ 40 mm Hg (before: 1.24 ± 0.03 ; after: 0.60 ± 0.02), RVSP 30-40 mm Hg (before: 0.87 ± 0.03 ; after: 0.41 ± 0.02), RVSP < 30 mm Hg (before: 0.65 ± 0.02 ; after: 0.32 ± 0.02), $P < 0.0001$ (Fig. 6D, E). Patients with no RVSP had a similar rate of hospitalization before and after the index echocardiography (before: 0.87 ± 0.02 ; after:

Figure 4. Box whiskers (1 to 99 percentile) plot of echocardiography parameters. Patients are divided into 4 groups based on their RVSP value. (A) Patients with higher RVSP tend to be older. Patients with no RVSP were mainly had insufficient tricuspid regurgitation (TR). (B) Left ventricular ejection fraction decreases with increasing RVSP. (C) Right ventricular (RV) diastolic dimension increases with increasing RVSP. (D) Right atrial (RA) volume index increases with increasing RVSP. (E) Tricuspid annular plane systolic excursion (TAPSE) decreased in the RVSP ≥ 40 mm Hg group. (F) TAPSE to RVSP ratio increased with increasing RVSP.

Figure 5. Clinical profile of patients. **(A)** Prevalence of ICD-10 diagnosis of PH increases with increasing RVSP. **(B)** The percentage of patients who had a right heart catheterization (RHC) increased with increasing RVSP. **(C)** Charlson Comorbidity Index (CCI); hospitalization 1 year before **(D)** and **(E)** 1 year after the echocardiography date with increasing RVSP and patients with no RVSP has the same level of CCI compared with patients with RVSP 30 to 40 mm Hg.

Figure 6. Distribution of comorbidities according to World Health Organization (WHO) PH classification. The prevalence of associated comorbidities in WHO groups 1, 2, 3, and 4 PH with (A) no RVSP, (B) RVSP < 30 mm Hg, (C) RVSP 30-40 mm Hg, and (D) RVSP ≥ 40 mm Hg. The total amount of comorbidity increases with increasing RVSP.

0.41 ± 0.02) compared with patients with RVSP between 30 and 40 mm Hg (Fig. 6D, E).

Examining comorbidities divided by WHO PH groups showed that patients with higher RVSP also had a higher cumulative amount of comorbidities (Fig. 3). Patients with comorbidities associated with group 2 PH were the most common, comprising 23.3% patients with no RVSP, 21.7% patients with RVSP < 30 mm Hg, 26.5% patients with RVSP between 30 and 40 mm Hg, and 30.8% patients with RVSP ≥ 40 mm Hg (Fig. 3A-D). The percentage of patients with comorbidities associated with group 1 and 4 PH was similar across all 4 RVSP groups (Fig. 3). Patients with comorbidities associated with more than 1 PH group experienced the largest increase with increasing RVSP (Fig. 3B-D). As a result, the proportion of patients with no PH-associated comorbidities decreased with increasing RVSP from 63.7% in patients with RVSP < 30 mm Hg to 50.1% in patients with RVSP between 30 and 40 mm Hg, and to 29.4% in patients with RVSP ≥ 40 mm Hg (Fig. 3B-D).

Clinical profile of patients with RVSP ≥ 30 and < 40 mm Hg

Given the recent update to the definition of PH, a subgroup analysis of patients with RVSP ≥ 30 and < 40 mm Hg

was performed dividing the group into quartiles (Fig. 7). The ICD-10 diagnosis of PH was 2 to 3 times higher in quartile 4 of the RVSP 30-40 group (Q_{430-40}) compared with the other 3 quartiles in RVSP 30-40 group and higher compared with patients with RVSP < 30 mm Hg (Fig. 7A). A similar pattern was seen in the percentage of patients who had RHC (Fig. 7B). The CCI was also significantly higher in Q_{130-40} compared with patients with RVSP < 30 mm Hg (1.10 ± 0.07 vs 0.84 ± 0.03 , $P = 0.04$) (Fig. 7C). Although the CCI was higher in Q_{330-40} (1.30 ± 0.08) and Q_{430-40} (1.31 ± 0.08) compared with Q_{130-40} (1.10 ± 0.07) and Q_{230-40} (1.08 ± 0.08), the difference was not significant. The number of hospitalizations 1 year before the index echocardiography increased with increasing RVSP, but it was not significant between Q_{130-40} and patients with RVSP < 30 mm Hg (0.70 ± 0.04 vs 0.65 ± 0.02) (Fig. 7D). However, the number of hospitalizations 1 year after index echocardiography increased with increasing RVSP, but only Q_{430-40} was significantly higher than in patients with RVSP < 30 mm Hg (0.49 ± 0.05 vs 0.32 ± 0.02 , $P = 0.004$) (Fig. 7E).

Discussion

This study has 3 main findings: (1) The prevalence of elevated RVSP ≥ 40 mm Hg (22.1%) and RVSP ≥ 30 and

Figure 7. Clinical profile of patients with RVSP ≥ 30 and < 40 mm Hg divided into quartiles. **(A)** Prevalence of ICD-10 diagnosis of PH. **(B)** Percent of patients with RHC. **(C)** CCI increases with increasing RVSP in the 30 to 40 mm Hg range and was significantly higher compared with patients with RVSP < 30 mmHg; the number of hospitalizations **(D)** 1 year before and **(E)** 1 year after the echocardiography date increases with increasing RVSP starting at 30 mm Hg.

< 40 mm Hg (22.0%) on echocardiography is more common than a clinical diagnosis of PH based on ICD-10 codes (3.1%); (2) elevated RVSP is associated with dilatation of right atrium and ventricle and reduced TAPSE; and (3) increasing RVSP > 30 mm Hg is correlated with increasing burden of comorbidities, higher number of hospitalizations, and higher likelihood of carrying a diagnosis of PH.

The prevalence of elevated RVSP ≥ 40 mm Hg in our cohort is 22.1%. This number was higher compared with other published studies, approximately 14% in the study by Maron et al.,²⁴ 9.1% in the study by Strange et al.,⁵ and 18.7% in the study by Strange et al.¹⁶ The higher prevalence of patients with elevated RVSP ≥ 40 mm Hg probably reflects the regional demographics of patients referred for imaging at KHSC. KHSC is the only tertiary care center in the South East Local Health Integration Network (LHIN), which serves the southeast region of Ontario, Canada. As of 2015, this region is home to approximately 495,000 people, which accounts for 3.6% of the population of Ontario.²⁵ Among the 14 LHINs in Ontario, the South East LHIN has the highest proportion of adults aged ≥ 65 years (21% of the population).²⁶ The South East LHIN is also the most rural LHIN in

southern Ontario, with 45% of the population living in rural areas.²⁶ Only 3.4% of South East LHIN residents are visible minorities, and most residents (79%) were born in Ontario.²⁶ In 2013 to 2014, comorbidities that predispose to PH were common, including systemic hypertension (22.8%; 95% confidence interval [CI], 20.7-25.0), heart disease (6.4%; 95% CI, 5.4-7.4), and chronic obstructive pulmonary disease (6.4%; 95% CI, 4.9-7.9).²⁶ This demography may delay presentation leading to capture of more patients with PH.

The percentage of patients (33%) who did not have documented RVSP, most commonly due to insufficient tricuspid regurgitation, was comparable to what Strange et al.⁵ found in their study (32%). The prevalence of ICD-10 diagnosis of PH in patients who did not have documented RVSP is 0.58% in our cohort, but O'Leary et al.²⁷ reported in a population of patients referred for RHC, PH was diagnosed in 47% of patients who had no RVSP because of lack of measurable tricuspid regurgitation velocity. This difference highlights the importance of pretest probability, because patients referred for RHC have a higher pretest probability of having PH than patients referred for a general echocardiography study. This being said, patients with no RVSP do not

necessarily rule out the presence of elevated RVSP. Patients with no RVSP have a higher amount of PH-related comorbidities (45.8%) than patients with RVSP < 30 mm Hg (36.3%) (Fig. 3A, B), which could explain why patients with no RVSP have a higher number of hospitalizations (1 year before: 0.87 ± 0.02 ; 1 year after: 0.41 ± 0.02) than patients with RVSP < 30 mm Hg (1 year after: 0.65 ± 0.02 ; 1 year after: 0.32 ± 0.02) (Fig. 6D, E).

Even when the echocardiography report states the patient has an elevated RVSP (≥ 40 mm Hg), PH is rarely listed as an ICD-10 diagnosis. In our study of patients with RVSP ≥ 40 mm Hg, only 11.7% of patients had a diagnosis of PH (Fig. 6A). This is consistent with Maron et al.,²⁴ who noted that only one-fifth of patients with RVSP ≥ 60 mm Hg had PH listed as a diagnosis in the medical record. These data suggest that PH remains under-reported.

Increasing RVSP is associated with increased RA-volume index and RV diastolic dimension, and decreased TAPSE and left ventricular ejection fraction (Supplemental Fig. S1). Sallach et al.¹³ showed that RA-volume index ≥ 30.6 mL/m² had a 78% sensitivity and a 77% specificity ($P < 0.0001$) for predicting RV systolic dysfunction stage ≥ 3 (tricuspid E/A ratio ≥ 2).¹³ RA-volume index ≥ 37.8 mL/m² had a 80% sensitivity and 80% specificity ($P = 0.0002$) for predicting RV diastolic dysfunction stage ≥ 3 .¹³ In our study, the mean (standard deviation) RA-volume index for patients with RVSP ≥ 40 mm Hg was 32.7 ± 0.4 mL/m². TAPSE is a well-accepted parameter to measure RV function. According to the guideline provided by the American Society of Echocardiography, TAPSE < 1.6 cm is considered abnormal.²¹ TAPSE was significantly decreased only in patients with RVSP ≥ 40 mm Hg. TAPSE was not significantly different among patients with RVSP between 30 and 40 mm Hg and less than 30 mm Hg, suggesting TAPSE is a late finding in the natural history of PH, which is consistent with existing evidence.²⁸ Dilatation of RA and RV likely preceded the decrease in TAPSE. The TAPSE/RVSP ratio has the highest correlation with clinical outcomes including the number of hospitalizations and CCI (Supplemental Fig. S1). Similar to what Guazzi et al.¹⁵ found in their study of 387 patients, our data also showed that lower TAPSE/RVSP is associated with worse outcome. In the study by Guazzi et al.,¹⁵ patients in tertile 1, who had the lowest TAPSE/RVSP < 0.35, had the worst clinical outcomes and highest mortality. In our study population, patients with RVSP ≥ 40 mm Hg has a mean TAPSE/RVSP ratio of 0.39 ± 0.13 mm Hg.

The updated definition of PH decreased mPAP from ≥ 25 mm Hg to > 20 mm Hg.³ On the basis of this updated definition, we examined patients with echocardiographic measurement of RVSP between > 30 and ≤ 40 mm Hg. Examining patients with RVSP ≥ 30 and < 40 mm Hg showed that 22.0% patients of the study population is in this group, which is almost equal to the number of patients in the RVSP ≥ 40 mm Hg (22.1%). Although hospitalization was not significantly higher in Q1₃₀₋₄₀ (RVSP 30-32.1 mm Hg) compared with patients with RVSP < 30 mm Hg, CCI was significantly higher in Q1₃₀₋₄₀ compared with patients with RVSP < 30 mm Hg ($P = 0.04$). Strange et al.¹⁶ showed that RVSP ≥ 30 mm Hg predicts increased short- and long-term mortality. Although we do not have direct measurement for mortality, significantly higher CCI and the increased

hospitalizations in the RVSP ≥ 30 and < 40 mm Hg group suggest that our data are congruent with Strange et al.¹⁶ Different from the work by Strange et al., which focuses on mortality, our study focuses on the patients' clinical profiles, which include comorbidities burden, hospitalization rate, and percent of RHC.

Limitations

This study uses the ICD-10 codes from the KHSC administrative database. The current diagnostic coding system (ICD-10) does not allow us to assign patients to a specific PH subgroup, which is a limitation of population-based surveys of PH. Unlike hypertensive diseases that are well classified and have their own category under disease of the circulatory system and 14 specific diagnostic codes, PH is a subsection of other pulmonary heart disease and only has 2 codes: (1) I27.0 primary PH and (2) I27.2 other secondary PH.²⁹ As a result, we have to rely on other diagnostic codes related to comorbidities of each subgroup of PH to determine a probable best fit categorization of patients into WHO PH groups. Although the most common isolated PH group in our study was group 2 PH, most patients with a diagnosis of PH (60.6%) had multiple comorbidities (most commonly the combination of chronic lung disease and left heart disease). Thus, they were classified as "mixed PH etiology." This was previously studied by our groups using population-level data from Ontario, Canada.¹⁸ Another limitation of our work is the lack of mortality data. The 1-year mortality from our previously published work was 36.4% with the diagnosis of PH,¹⁸ anticipating more deaths with those with a higher CCI and higher RVSP. Although this would underestimate our hospitalisation rates, especially in those with an RVSP > 30 mm Hg, the main findings discussed would remain valid.

Conclusions

RVSP ≥ 40 mm Hg in patients is prevalent (22.1%), and lowering the threshold to ≥ 30 mm Hg based on the updated definition doubles the prevalence to 44.1%. Elevated RVSP ≥ 30 mm Hg portends a poor prognosis, evident as increased CCI and hospitalizations. Our results showed that RVSP can be viewed as a noninvasive marker to risk stratify patients, particularly when combined with other echocardiographic parameters, such as RA-volume index, RV diastolic dimension, and TAPSE, along with patients' clinical profile using comorbidities, such as systolic/diastolic dysfunction, connective tissue diseases, and sleep-disordered breathing. Quantitatively analyzing patients' echocardiographic and clinical comorbidities could facilitate early diagnosis of PH, initiation of referral to PH specialist, and therapy. Facilitating recognition of even mild elevation of RVSP is the first step in mitigating adverse outcomes of this emerging epidemic of PH.

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Disclosures

The authors have no conflict of interest to disclose.

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Supplementary Material

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