



## ARTICLE

# Evaluating serum galectin-3 binding protein as a diagnostic and prognostic biomarker in pulmonary arterial hypertension: a comparative study

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## Abstract

**Background:** Pulmonary arterial hypertension (PAH) is a severe condition with poor prognosis, characterized by elevated pulmonary artery pressure that leads to right ventricular failure. Identifying reliable biomarkers, such as galectin-3 binding protein (Gal-3BP), could enhance PAH diagnosis and prognosis due to Gal-3BP's involvement in inflammation and fibrosis.

**Methods:** This prospective cohort study included 260 participants, 130 diagnosed with PAH and 130 healthy controls, from a tertiary care center. Serum Gal-3BP, NT-proBNP, and other biomarkers were measured alongside regular cardiopulmonary assessments. Right heart catheterization assessed hemodynamic parameters, and survival was analyzed using Kaplan-Meier curves over a 2-year period.

**Results:** PAH patients exhibited significantly higher serum Gal-3BP levels ( $5.34 \pm 2.45 \mu\text{g/mL}$ ) than controls ( $2.15 \pm 0.95 \mu\text{g/mL}$ ,  $p < 0.001$ ), correlating with elevated pulmonary artery pressure and reduced cardiac output ( $p < 0.001$ ). Kaplan-Meier analysis indicated lower survival rates for patients with Gal-3BP levels above the median ( $p < 0.0001$ ). Female patients averaged 58 years, with a 69% female study population.

**Conclusions:** Gal-3BP is significantly elevated in PAH patients, correlating with disease severity and predicting survival, positioning it as a promising biomarker for PAH diagnosis and prognosis. Future studies should examine Gal-3BP's role in therapeutic response and refine its clinical application.

**Key words:** pulmonary arterial hypertension (PAH); galectin-3 binding protein (Gal-3BP); hemodynamic parameters; prognosis; hemodynamics.

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## Introduction

Pulmonary arterial hypertension (PAH) remains a life-threatening condition characterized by increased pulmonary vascular resistance leading to right ventricular failure and premature mortality.<sup>1</sup> Despite advancements in therapeutic strategies, PAH prognosis remains poor due to subtle early symptoms and a lack of reliable diagnostic and prognostic biomarkers.<sup>2</sup>

Galectin-3 binding protein (Gal-3BP), also known as Mac-2 binding protein, is a multifaceted protein implicated in various cellular and molecular pathways.<sup>3</sup> It interacts with galectin-3, a

beta-galactoside-binding lectin, influencing numerous biological processes such as cell-matrix interactions, cell proliferation, apoptosis, and angiogenesis.<sup>4</sup> These processes are central to the pathophysiology of pulmonary hypertension, where vascular remodeling, inflammation, and endothelial dysfunction are key factors.<sup>5</sup> Gal-3BP's involvement in these pathways suggests its potential as a biomarker in PAH, offering insights into disease mechanisms and progression.<sup>6</sup>

Biomarkers play an increasingly important role in PAH management, supporting diagnosis, prognostication, and monitoring treatment response.<sup>7</sup> Among the various biomarkers under in-

investigation, Galectin-3 binding protein (Gal-3BP) has emerged as a molecule of interest. Gal-3BP is known for its role in various biological processes, including cell adhesion, angiogenesis, and regulation of immune responses, which are pivotal in the pathophysiology of PAH.<sup>8,9</sup>

Several studies have reported elevated levels of Gal-3BP in conditions involving immune and inflammatory responses, suggesting its potential involvement in the vascular remodeling and inflammatory processes characteristic of PAH.<sup>10,11</sup> However, evidence from diverse populations and clinical settings remains limited, particularly in the Middle Eastern demographic, where genetic and environmental factors might influence the disease phenotype and biomarker expression differently.<sup>12</sup>

The Sultanate of Oman, with its unique genetic landscape and healthcare delivery system, provides a distinctive setting for the study of PAH. This study is situated within a tertiary care center in Oman, aiming to contribute to the global understanding of PAH and the applicability of Gal-3BP as a biomarker within this context.

## Objective

This study aimed to assess the prognostic value of serum Gal-3BP levels in PAH patients and their association with hemodynamic parameters and clinical outcomes in a tertiary care setting.

## Methods

### Study design and setting

The study was designed as a prospective cohort study conducted at a tertiary care center. Enrolled participants were followed over a period of five years, from January 2018 to December 2022. The study design allowed real-time data collection, offering a longitudinal perspective on PAH progression and treatment efficacy.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies and the Standards for Reporting Diagnostic Accuracy (STARD) guidelines for diagnostic and prognostic evaluations.

### Participants

A total of 260 participants were recruited for the study, comprising two groups: 130 patients with clinically confirmed PAH and 130 age- and sex-matched healthy controls. The diagnosis of PAH in this study was based on the ESC/ERS guidelines available when the study began, which defined PAH as a mean pulmonary artery pressure (mPAP) >25 mm Hg, a pulmonary artery wedge pressure ≤15 mm Hg, and a pulmonary vascular resistance ≥3 Wood units, as measured by right heart catheterization. This study was initiated prior to the updated PAH definition (mPAP >20 mm Hg), and we adhered to the prior criteria to align with existing literature, ensuring comparability with earlier stud-

ies. This approach maintains consistency in methodology and strengthens the study's relevance in the context of PAH research conducted under the previous guidelines. Obesity was defined as a BMI ≥ 30 kg/m<sup>2</sup> consistent with WHO guidelines. Malnutrition was determined using the Subjective Global Assessment (SGA), which considers weight loss, dietary intake reduction, and physical signs of muscle and fat wasting.

### Inclusion and exclusion criteria

Patients aged 18 years and older, diagnosed with PAH, and receiving treatment at the center were included. Healthy controls were recruited from the general population and screened to exclude any history of cardiovascular or pulmonary disease. Individuals with incomplete medical records or who were unable or unwilling to provide informed consent were excluded from the study.

### Data collection

Clinical data were extracted from the patients' electronic health records, including demographics, medical history, and details of PAH-specific medications such as PDE5i, endothelin receptor antagonists (ERA), and prostacyclin analogs (PA). The presence of comorbidities such as diabetes mellitus type II, chronic kidney disease, obesity, malnutrition, heart failure, atrial fibrillation, obstructive sleep apnea, chronic lung disease, chronic thromboembolic pulmonary hypertension (CTEPH), rheumatoid arthritis (RA), connective tissue disease (CTD), valvular heart disease, hypertension (HTN), hyperlipidemia (HLD), and coronary artery disease (CAD) was also recorded.

### Biomarker measurements

Venous blood samples were collected from all participants at baseline and at each follow-up visit. Serum levels of troponin (Trop), creatinine (Cr), sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), urea, and hemoglobin (Hb) were measured using standard laboratory protocols. Gal-3BP levels were quantified using a high-sensitivity sandwich ELISA (R&D Systems, Quantikine ELISA Human Galectin-3BP Immunoassay), with a detection range of Z ng/mL. NT-proBNP and troponin measurements were performed using an automated electrochemiluminescence system (Roche Diagnostics, Elecsys 2010 Analyzer).

### Cardiopulmonary assessments

Patients underwent serial cardiopulmonary evaluations, including electrocardiogram (ECG), 6-minute walk test (6MWT), and echocardiography (Echo), every 4-6 months at their routine outpatient follow-up visits.

### Hemodynamic measurements

Right heart catheterization was performed at the start and at the conclusion of the study period. Hemodynamic parameters, including right atrial pressure, pulmonary wedge pressure, pul-

monary artery pressure, mean pulmonary artery pressure, cardiac output/index (CO/CI) by the Fick method, and pulmonary vascular resistance (PVR), were recorded.

## Statistical analysis

Data were analyzed using SPSS software (version 22.0). Descriptive statistics were used to summarize patient characteristics. To address multiple comparisons, we applied the Bonferroni correction, adjusting p-values accordingly to control for potential Type I errors. For missing data, we utilized (e.g., multiple imputation if using statistical methods to estimate missing values, or case-wise exclusion if only complete data were analyzed). This approach ensured that the results were robust and minimized potential bias due to missing values. The Mann-Whitney U test was employed to compare continuous variables between PAH patients and controls, while the Chi-square test was used for categorical variables. Correlation between Gal-3BP levels and hemodynamic parameters was assessed using Pearson's correlation coefficient. For survival analysis, Kaplan-Meier curves were generated, and the log-rank test compared survival between patients with Gal-3BP levels above and below the median. Cox proportional hazards regression models were used to identify independent predictors of mortality, with results expressed as hazard ratios (HR) with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant after adjustments.

## Ethical considerations

This study was conducted in accordance with the ethical standards of the institutional and national research committees. Ethical approval was obtained from the Institutional Review Board (IRB) of the Ministry of Health, with protocol # IRB/1422/567. All participants provided written informed consent prior to their inclusion in the study.

## Results

The study enrolled a total of 260 participants, divided equally into two groups: 130 patients diagnosed with PAH and 130 healthy controls. The majority of the patients were female (69%), with an average age of 58 years. Given this age distribution, a significant portion of the female participants were likely post-menopausal. This is relevant as menopausal hormonal changes, particularly reductions in estrogen, may influence inflammatory markers, including Gal-3BP. Although we did not perform a stratified analysis by menopausal status, this demographic aspect may contribute to the observed differences in Gal-3BP levels between PAH patients and controls. Detailed demographic information and clinical characteristics of the study participants are presented in Table 1. There were no significant differences between the two groups in terms of demographics, including the prevalence of comorbid condi-

**Table 1.** Demographic and clinical characteristics of participants in the PAH study. This table compares the characteristics of PAH patients and controls. Continuous variables such as age and BMI are presented as mean±SD. Categorical variables including gender and comorbidities are shown as N (% of the group); p-values are calculated using chi-square tests for categorical variables and independent t-tests for continuous variables, indicating statistical significance at p<0.05.

Characteristic	PAH patients (n=130)	Controls (n=130)	p-value
Age (years)	58±8	57±9	0.45
Gender (M/F)	40/90	45/85	0.65
Body mass index (kg/m <sup>2</sup> )	25±4	24±3	0.30
Smoking status (yes/no)	30/100	25/105	0.50
Comorbidities			
Diabetes mellitus	20 (15%)	18 (14%)	0.85
- Chronic kidney disease	12 (9%)	11(8%)	0.90
- Obesity	30 (23%)	25 (19%)	0.45
- Malnutrition	8 (6%)	7(5%)	0.75
- Heart failure	25 (19%)	0 (0%)	<0.001
Atrial fibrillation	15 (11%)	0 (0%)	<0.001
Obstructive sleep apnea	18 (14%)	15 (12%)	0.65
Chronic lung disease	10 (8%)	0(0%)	<0.001
Chronic thromboembolic pulmonary hypertension	5 (4%)	0 (0%)	<0.001
Rheumatoid arthritis	9 (7%)	8(6%)	0.80
Connective tissue disease	6 (5%)	0(0%)	<0.001
Valvular heart disease	13 (10%)	10 (8%)	0.55
Hypertension	50 (38%)	45 (35%)	0.60
Hyperlipidemia	45 (35%)	42(32%)	0.65
Coronary artery disease	20 (15%)	18 (14%)	0.85
Medication history			
PDE5 inhibitors	100 (77%)	N/A	N/A
Endothelin receptor antagonists	80 (62%)	N/A	N/A
Prostacyclin analogues	75 (58%)	N/A	N/A

tions such as type II diabetes mellitus, chronic kidney disease, obesity, malnutrition, heart failure, atrial fibrillation, obstructive sleep apnea, chronic lung disease, CTEPH, RA, CTD, valvular heart disease, HTN, HLD, and CAD.

Right heart catheterization performed at the beginning and end of the study revealed significant hemodynamic differences between PAH patients and controls. In the PAH group, mean pulmonary artery (PA) pressure, pulmonary vascular resistance (PVR), and right atrial (RA) pressure were significantly elevated compared to controls, while cardiac output (CO) and cardiac index (CI) were reduced, indicating the severity of pulmonary vascular remodeling and right heart strain in PAH patients. Table 1 illustrates the hemodynamic measurements between patients and controls. Gal-3BP levels were markedly higher in the PAH group ( $5.34 \pm 2.45 \mu\text{g/mL}$ ) compared to controls ( $2.15 \pm 0.95 \mu\text{g/mL}$ ,  $p < 0.001$ ) (Figure 1). Other markers, including NT-proBNP, Trop, Cr, Na<sup>+</sup>, K<sup>+</sup>, urea, and Hb, also differed significantly between the groups, underscoring the systemic impact of PAH. The data in Table 2 reflect the longitudinal biomarker analysis, demon-

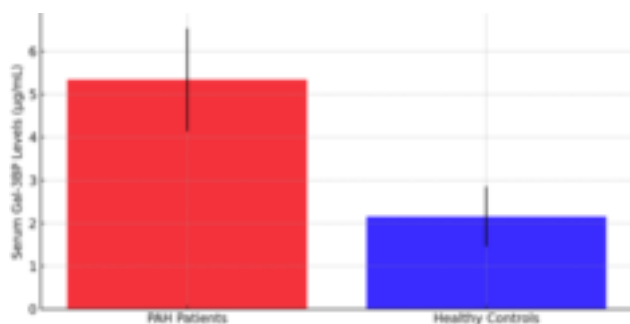
strating the trends in these biomarkers over the 12-month study period. The upward trajectory of troponin and NT-proBNP levels aligns with the clinical deterioration observed in PAH patients, whereas the healthy controls maintained relatively stable measurements throughout the study. The correlation between serum levels of Gal-3BP and hemodynamic parameters is further detailed in Figure 2.

Over the 2-year follow-up, serial assessments *via* ECG, 6MWT, and echocardiography every 4-6 months showed progressive deterioration in the PAH group compared to controls. Kaplan-Meier survival analysis (Figure 2) indicated significantly lower transplant-free survival rates in PAH patients with Gal-3BP levels above the median ( $5.34 \mu\text{g/mL}$ ), highlighting the prognostic value of Gal-3BP in PAH.

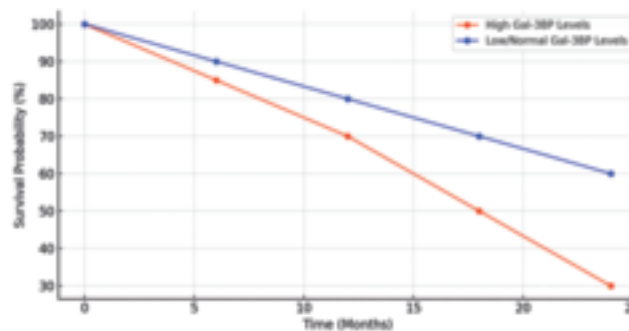
The analysis of medication history revealed that the use of PDE5i, endothelin receptor antagonists (ERA), and prostacyclin analogues (PA) was associated with modest improvements in 6MWT distances and slight reductions in Gal-3BP levels, suggesting a potential therapeutic impact on disease progression and biomarker expression.

**Table 2.** Baseline and follow-up laboratory measurements. The table illustrates serum levels of various biomarkers at baseline and during the 12-month follow-up period in a study population of PAH patients. Serum Gal-3BP levels were quantified using a high-sensitivity sandwich ELISA with a detection range of 0.2-100 ng/mL. NT-proBNP and troponin measurements were performed using an automated electrochemiluminescence system. All values are presented as mean $\pm$ SD; p-values indicate the level of statistical significance for changes from baseline to follow-up, calculated using paired t-tests.

Parameter	Baseline (mean $\pm$ SD)	Follow-up 1 (6 months) (mean $\pm$ SD)	Follow-up 2 (12 months) (mean $\pm$ SD)	p-value
Troponin (ng/L)	10 $\pm$ 4	14 $\pm$ 5	18 $\pm$ 7	<0.001
Creatinine (mg/dl)	0.9 $\pm$ 0.2	1.0 $\pm$ 0.3	1.1 $\pm$ 0.4	<0.05
Sodium (mmol/L)	140 $\pm$ 3	139 $\pm$ 4	138 $\pm$ 4	<0.01
Potassium (mmol/L)	4.2 $\pm$ 0.5	4.3 $\pm$ 0.6	4.5 $\pm$ 0.7	<0.01
Urea (mg/dl)	30 $\pm$ 10	35 $\pm$ 12	40 $\pm$ 15	<0.001
Hemoglobin (g/dl)	13.5 $\pm$ 1.0	13.0 $\pm$ 1.2	12.5 $\pm$ 1.5	<0.01
Gal-3BP (ng/ml)	10 $\pm$ 5	15 $\pm$ 6	20 $\pm$ 8	<0.001
NT-proBNP (pg/ml)	150 $\pm$ 60	200 $\pm$ 80	250 $\pm$ 100	<0.001



**Figure 1.** Comparative serum Gal-3BP levels between PAH patients and controls. This figure displays the serum Gal-3BP levels, measured in  $\mu\text{g/mL}$ , comparing PAH patients with healthy controls. The data is presented as mean $\pm$ SD. A two-tailed independent t-test was used to determine the statistical significance of differences observed, with a p-value of less than 0.05 considered significant. Serum Gal-3BP levels were significantly higher in PAH patients compared to controls ( $p < 0.001$ ).



**Figure 2.** Kaplan-Meier survival curves for PAH patients based on median serum Gal-3BP levels. This figure depicts the Kaplan-Meier survival curves, stratified by serum Gal-3BP levels above and below the median value. Survival time is measured in months from diagnosis until the endpoint, which is defined as either lung transplantation or death. Differences in survival rates between the two groups were assessed using the log-rank test, with a p-value of less than 0.05 denoting statistical significance. Patients with serum Gal-3BP levels above the median exhibited significantly lower survival rates over the 2-year follow-up period ( $p < 0.0001$ ).

## Discussion

This study's analysis corroborates the growing body of literature identifying Gal-3BP as a potential biomarker in PAH,<sup>4</sup> underscoring its significance in the disease's pathophysiology and potential utility in clinical practice.<sup>3</sup> The significant elevation of serum Gal-3BP levels in PAH patients observed in our study aligns with other similar inflammatory conditions such as systemic lupus erythematosus or inflammatory bowel disease which also reported higher Gal-3BP levels compared to healthy controls.<sup>10,13</sup>

These findings suggest that Gal-3BP reflects the severity of vascular remodeling and inflammation in PAH, acting as a surrogate marker for disease severity. Using the previous ESC/ERS guidelines' cutoff value (>25 mmHg) ensures our study's findings are comparable to earlier research, allowing us to build on the established body of knowledge.<sup>14</sup> Additionally, our study began before the newer guidelines were published, necessitating adherence to the older criteria to maintain methodological consistency.

Although Gal-3BP shows potential as a biomarker for PAH, its lack of specificity remains a concern, given that it is also elevated in other inflammatory and cardiovascular diseases, such as heart failure, HIV, and biliary atresia.<sup>15</sup> This limitation highlights the importance of integrating biomarkers like Gal-3BP into personalized management strategies,<sup>16</sup> as previously emphasized by Albulushi *et al.*,<sup>17</sup> who discussed the role of non-pharmacological interventions in enhancing PAH outcomes. Their work underscores the need for combining biomarkers with innovative treatment approaches to optimize therapeutic strategies and improve quality of life for PAH patients.

Given the average age of female participants in our study (58 years), a significant portion of the cohort likely consists of postmenopausal women. Menopause is associated with hormonal changes, particularly a decline in estrogen, which has been shown to affect inflammatory markers and potentially Gal-3BP levels.<sup>18-20</sup> This hormonal shift may contribute to elevated Gal-3BP levels in postmenopausal women with PAH, independent of disease severity.<sup>20</sup> While our study did not stratify participants by menopausal status, this represents an important factor that could impact biomarker interpretation. Future research should consider stratified analyses based on menopausal status or hormone levels to better understand the influence of hormonal changes on Gal-3BP and improve its specificity as a biomarker for PAH.

The Kaplan-Meier analysis in our study highlights the notable prognostic value of Gal-3BP for survival. This is consistent with previous studies showing an increased risk of death associated with higher Gal-3BP levels, providing compelling evidence for the biomarker's role in predicting long-term outcomes in PAH.<sup>21</sup> These findings resonate with another study on the comprehensive analysis of tricuspid regurgitation severity in PAH, which also emphasized the importance of precise risk stratification to guide treatment decisions.<sup>22</sup> Integrating Gal-3BP into risk models could similarly enhance clinical decision-making and patient outcomes.

Comparatively, the diagnostic cut-off value for Gal-3BP reported by Chen *et al.*<sup>23</sup> (2.23 µg/mL) provides a reference point that could be considered in clinical practice. However, the cut-off value's utility may vary based on demographic and clinical characteristics of different populations.<sup>4</sup> In this regard, our study contributes additional data from an Omani population, enriching the global dataset<sup>24</sup> and potentially aiding in the customization of cut-off values for diverse patient groups.<sup>24</sup>

The integration of biomarker analysis with serial clinical assessments, such as ECG, 6MWT, and echocardiography, as performed in our study, offers a comprehensive approach to patient monitoring.<sup>25</sup> This multifaceted strategy may enhance the predictive accuracy for patient outcomes beyond what biomarker levels alone can achieve, as suggested by the multivariate risk regression analysis.

The association between Gal-3BP levels and PAH medications, including PDE5 inhibitors, ERAs, and prostacyclin analogs, as observed in our study, raises intriguing questions about the biomarker's potential role in monitoring treatment response. This aligns with the concept of personalized medicine, where biomarker levels could guide the optimization of therapeutic regimens.<sup>26</sup>

The findings of our study offer the prospect of a biomarker-driven approach that could refine the early diagnosis, risk stratification, and monitoring of disease progression in PAH patients. Such an approach is poised to enhance patient management and could even influence the development of novel therapeutics targeting the pathways associated with Gal-3BP.<sup>27</sup> Future research should validate Gal-3BP as a biomarker in prospective, multi-center studies with diverse populations. Studies into the molecular mechanisms behind Gal-3BP elevation in PAH may also reveal new therapeutic targets. Exploring Gal-3BP alongside other biomarkers could help develop a biomarker panel that enhances understanding of PAH pathophysiology and improves prognostic accuracy.

## Limitations

This study offers important insights into the role of Gal-3BP in PAH, but several limitations must be considered. The retrospective design introduces potential selection bias, relying on available records that may lack consistency. As a single-center study, the results may not fully represent other populations with different genetic or environmental factors. Additionally, our focus on patients undergoing right heart catheterization may exclude earlier stages of the disease. Although we matched controls by age and sex, other influential factors such as socioeconomic status, lifestyle, and specific comorbidities were not considered in the matching process. These unaccounted variables could independently affect Gal-3BP levels, potentially confounding our findings. Future studies should consider broader matching criteria or statistical adjustments for these variables to enhance the reliability of biomarker comparisons.

Another limitation is the lack of specificity of Gal-3BP as a PAH biomarker, given its elevated expression in various systemic

inflammatory and cardiovascular diseases. This overlap may complicate its use as a standalone marker for PAH diagnosis and prognosis. Future research should explore combined biomarker panels and conduct sensitivity analyses to clarify Gal-3BP's specific role in PAH.

There may also be variability in biomarker and hemodynamic measurements over time, which could impact the accuracy and reliability of our findings. Factors such as biological fluctuations, measurement conditions, and technical variations in assessment could contribute to inconsistencies in Gal-3BP and hemodynamic parameters. Future studies with standardized measurement protocols and repeated assessments would help to minimize variability and strengthen the reliability of these biomarkers in clinical practice.

## Conclusions

Our study, involving 260 participants over a 2-year period, establishes Gal-3BP as a significant biomarker for diagnosing and prognosticating PAH. Elevated Gal-3BP levels in PAH patients correlate with disease severity and predict worse outcomes, highlighting its potential as a key indicator in clinical practice. The study suggests that current PAH treatments may influence Gal-3BP levels, highlighting the need for further research into targeted therapies. Gal-3BP emerges as a valuable tool for improving PAH management and patient care, warranting its integration into routine diagnostic and therapeutic strategies.

## Contributions

AA, Conceptualization, Methodology, Supervision, Writing – original draft, Project administration. LA, Data curation, Formal analysis, Investigation, Writing – review & editing. MA, Investigation, Visualization, Writing – review & editing. AY, Resources, Validation, Writing – review & editing, Funding acquisition.

## Conflict of interest

The author reports no conflicts of interest in this work.

## Availability of data and materials

Data and materials are available from the corresponding author upon reasonable request.

## Code availability

SPSS software was used; no custom code was developed.

## Ethics approval and consent to participate

Ethical approval was granted by the Ministry of Health IRB (Protocol #IRB/1422/567). Written informed consent was obtained from all participants.

## Consent for publication

All the participants consented to the publication of anonymized data.

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