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Decrease of haemoconcentration reliably detects hydrostatic pulmonary oedema in dyspnoeic patients in the emergency department – a machine learning approach

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Abstract

Background Haemoglobin variation (ΔHb) induced by fluid transfer through the intestitium has been proposed as a useful tool for detecting hydrostatic pulmonary oedema (HPO). However, its use in the emergency department (ED) setting still needs to be determined.

Methods In this observational retrospective monocentric study, ED patients admitted for acute dyspnoea were enrolled. Hb values were recorded both at ED presentation (T_0) and after 4 to 8 h (T_1). ΔHb between T_1 and T_0 ($\Delta Hb_{T1\text{-}T0}$) was calculated as absolute and relative value. Two investigators, unaware of Hb values, defined the cause of dyspnoea as HPO and non-HPO. $\Delta Hb_{T1\text{-}T0}$ ability to detect HPO was evaluated. A machine learning approach was used to develop a predictive tool for HPO, by considering the ability of ΔHb as covariate, together with baseline patient characteristics.

Results Seven-hundred-and-six dyspnoeic patients (203 HPO and 503 non-HPO) were enrolled over 19 months. Hb levels were significantly different between HPO and non-HPO patients both at T_0 and T_1 ($p < 0.001$). $\Delta Hb_{T1\text{-}T0}$ were more pronounced in HPO than non-HPO patients, both as relative (-8.2 [-11.2 to -5.6] vs. 0.6 [-2.1 to 3.3] %) and absolute (-1.0 [-1.4 to -0.8] vs. 0.1 [-0.3 to 0.4] g/dL) values ($p < 0.001$). A relative $\Delta Hb_{T1\text{-}T0}$ of -5% detected HPO with an area under the receiver operating characteristic curve (AUROC) of 0.901 [0.896–0.906]. Among the considered models, Gradient Boosting Machine showed excellent predictive ability in identifying HPO patients and was used to create a web-based application. $\Delta Hb_{T1\text{-}T0}$ was confirmed as the most important covariate for HPO prediction.

Conclusions $\Delta Hb_{T1\text{-}T0}$ in patients admitted for acute dyspnoea reliably identifies HPO in the ED setting. The machine learning predictive tool may represent a performing and clinically handy tool for confirming HPO.

Keywords Pulmonary edema, Lung water, Haemoconcentration, Haemodilution, Augmented intelligence

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Background

Acute-onset dyspnoea is one of the leading symptoms for patients admission at the emergency department (ED) [1–3]. It is estimated to be responsible for up to five million ED visits each year in the United States [4] with 30-day mortality ranging from 8 to 13% [1, 5]. Thus, a rapid and precise identification of the underlying mechanisms is of utmost importance.

However, diagnosing the cause of dyspnoea and acute respiratory failure is often challenging in the setting of emergency. In particular, differential diagnosis between hydrostatic pulmonary oedema (HPO) and other causes of dyspnoea may be complicated, as symptoms and signs are non-specific and physical examination is often not decisive [2, 6, 7]. To discriminate them, emergency physicians need to integrate their clinical assessment with rapidly available investigations, such as chest radiograph, electrocardiogram, bedside lung and cardiac ultrasound and blood tests [3, 8–11]. Today, the diagnosis of HPO is mainly based on the dosage of the plasma level of B-type natriuretic peptide (BNP), which is costly and is affected by many factors such as inflammation, obesity and suffers from some false positives, especially in case of renal failure [12–14]. Moreover, there is a grey zone in which its plasmatic values are not informative [15].

Pathophysiologically, HPO is characterised by the filtration of protein-poor plasma through the pulmonary capillary barrier toward the *interstitium* [2, 16]. It has been demonstrated that this volume is large enough for inducing haemoconcentration, resulting in an increase of haematocrit, haemoglobin (Hb) or plasma protein concentration, reflecting the decrease in plasma volume and the volume of lung oedema [17, 18]. Such a haemoconcentration has been demonstrated to reliably diagnose weaning-induced pulmonary oedema, i.e. pulmonary oedema induced by switching patients from positive to negative pressure ventilation during a spontaneous breathing trial (SBT) in the intensive care unit (ICU) [19–21]. Nevertheless, the diagnostic accuracy of Hb changes in the ED setting for detecting HPO in a population of dyspnoeic patients still needs to be determined.

Methods

Patients

This retrospective, observational, monocentric study was conducted in the emergency department of a university hospital. Patients were included if (i) they were admitted to the ED for dyspnoea as leading problem, (ii) at least two Hb measurements were retrievable, one at ED admission before any treatment except oxygen was started, and one after 4 to 8 h. Patients were excluded if (i) no data regarding therapeutic management, radiological and biochemical investigations were retrievable and (ii) they were not subsequently admitted to an hospital ward. The study was approved by the Local Ethics Committee (Comitato Etico Territoriale Interaziendale AOU Maggiore della Carità di Novara, CE 93/20). Due to the retrospective nature of the study and the indications of the Ethic Committee, the need for an informed consent was waived.

Collected data and study design

At ED admission (T_0), we collected patients' demographic, past medical history with special attention to cardiac and respiratory comorbidities, and home therapy information. Data regarding physical examination and vital signs were also collected, including arterial blood pressure, heart rate, respiratory rate, peripheral oxygen saturation and body temperature.

Still at T_0, we collected blood samples for cellular blood count, biochemical variables including C-reactive protein (CRP), and arterial blood gas analysis (ABL90 FLEX, Radiometer Medical ApS, Copenhagen, Denmark). The value of Hb was collected from the arterial blood gas sample.

Other variables collected at T_0 included radiological investigations decided by clinicians in charge (chest X-ray, lung ultrasound or CT-scan) and, when available, ECG and transthoracic echocardiography performed by a cardiologist.

At 4 to 8 h from ED presentation (T_1), we again collected vital signs and blood samples data, including Hb. The difference between Hb values between T_1 and T_0 ($\Delta Hb_{T1\text{-}T0}$) was calculated, both as absolute ($(Hb_{T1}\text{-}Hb_{T0})$ and relative ($(Hb_{T1}\text{-}Hb_{T0})/Hb_{T0}*100$) change. At T_1, the treatment received between two timepoints, the destination of the patient and the retained diagnosis were also recorded. Finally, we collected the last value of Hb recorded before hospital discharge.

Data were retrieved from electronic medical record used in the ED (PsNet, Hi.Tech SpA, Firenze, Italy). All data were anonymised and uploaded on a Research Electronic Data Capture platform (REDCap consortium, Vanderbilt University, TN, USA), hosted at the Università del Piemonte Orientale.

Diagnosis of HPO

Two expert investigators (FG and LMC), unaware of changes in Hb values, defined *a posteriori* the cause of dyspnoea as HPO and non-HPO, by reviewing all patients' medical records. They particularly considered the past medical history (e.g., acute onset of dyspnoea), typical clinical signs of HPO (e.g., bilateral rales, orthopnoea, low-extremity pitting oedema), typical findings on chest X-ray, lung ultrasound (B-lines) and echocardiography - when performed - and absence of an obvious alternative diagnosis (e.g., pulmonary embolism at CT-scan with no infiltrates). The response to treatment of the

clinical, radiological and gas exchange abnormalities was also considered. For patients defined as non-HPO, the expert investigators made an alternative diagnosis. We planned to exclude patients with non-consensual diagnosis from analysis.

Statistical analysis

Sample size

In a previous study, ΔHb for diagnosing HPO provided an area under the receiver operating curve (AUROC) of 0.79 [19]. The sample size was determined for obtaining such an AUROC with a margin of error in the sample estimates of 0.026, as suggested in the literature [22]. A sample of 706 patients was necessary. This calculation was performed using R3.4.2 software [23].

Descriptive statistics

Data are reported as median [interquartile range] for continuous variables and percentages (absolute values) for qualitative variables. The Wilcoxon test was performed for comparing continuous variables and the Pearson's chi-square test (or Fisher's exact test where appropriate) for categorical ones. The diagnostic ability of both absolute and relative ΔHb_{T1-T0} for detecting HPO was evaluated by calculating the AUROC with the relative confidence intervals. A p-value of 0.05 was considered as the limit for significant effects. This statistical analysis was performed with MedCalc (Mariekerke, Belgium) and R3.4.2 software.

Machine learning models

A machine-learning approach was then considered to develop a predictive tool for HPO, by considering as a covariate the ability of ΔHb_{T1-T0}, together with baseline patient characteristics, such as age and sex, the presence of coronary artery disease, arterial hypertension, chronic obstructive pulmonary disease, cardiac valvular diseases or chronic renal failure. The algorithms used to train the model were the Random Forest (RF), Recursive Partitioning and Regression Trees (RPART), Gradient Boosting Machine (GBM), Support Vector Machine (SVM), and a Generalized Linear Model via Elastic Net penalized maximum likelihood (GLMNET). The characteristics of each model, the evaluation of their performance as well as the impact of each predictor on the model's performance are detailed in Supplementary Material 1.

Results

Patient characteristics

Between 1st June 2018 and 31st December 2019, 706 patients admitted to the ED with dyspnoea as leading problem were enrolled in the study. Among them, 203 were assigned to the HPO group and 503 to the non-HPO group. No differences were observed between the two groups in terms of gender distribution and age (Table 1). HPO patients showed a higher prevalence of cardiovascular diseases, such as arterial hypertension, dilated cardiopathy and coronary artery disease compared to the non-HPO ones. Also, for patients in whom it could be retrieved, left ventricular ejection fraction (LVEF) at T_0 was lower in the HPO group ($n=113$) compared to the non-HPO one ($n=211$) (49[38–57]% vs. 55[40–60]%, respectively; $p<0.001$). The remaining patient characteristics are detailed in Table 1.

Clinical, biological and radiological characteristics of HPO and non-HPO patients

HPO patients showed a significantly higher value of both systolic and diastolic arterial blood pressure at ED presentation compared to non-HPO patients (Table 2), whereas no differences were observed in terms of heart rate ($p>0.05$). The severity of respiratory impairment was similar between the two groups, both in terms of respiratory rate and arterial oxygenation, according to the arterial oxygen partial pressure over inspired oxygen fraction ratio (PaO_2/FiO_2) level (Table 2). One-hundred twenty-two patients underwent echocardiography at the ED. LVEF was significantly lower in the HPO ($n=61$) compared to the non-HPO patients ($n=61$) (36 [30–46]% vs. 50 [40–57]%, respectively; $p<0.001$).

Laboratory findings and first ED therapy

Non-HPO and HPO patients showed similar levels of plasma creatinine, sodium, and potassium values at baseline (Supplementary Material 2). However, HPO patients showed lower CRP levels compared to the non-HPO ones (1.64 [0.74–5.44] vs. 3.40 [0.99–9.83]mg/dL, respectively; $p<0.001$) and higher levels of BNP (2150 [1424–2675] vs. 273 [135–660]pg/mL, respectively; $p<0.001$). Of note, BNP values were available for only 135 (58 HPO and 77 non-HPO) patients (Supplementary Material 2). As for the initial therapy in the ED, patients with HPO were more likely to receive diuretics, nitrates, and continuous positive airway pressure (CPAP) over the first hour compared to non-HPO patients. On the other hand, non-HPO patients were more frequently treated with steroids, bronchodilators and antibiotics (Supplementary Material 3). The final diagnoses are reported in Supplementary material 4.

Haemoglobin values and changes over time

Hb level was significantly higher in HPO than in non-HPO patients at T_0 (Table 3). It significantly decreased from T_0 to T_1 in HPO patients, while it did not change significantly in non-HPO patients (Table 3). The time interval between T_0 and T_1 was similar among HPO and non-HPO patients (Table 3). ΔHb_{T1-T0} were more pronounced in HPO than non-HPO patients, both as relative

Table 1 Patient characteristics

	HPO (*n* = 203)	Non-HPO (*n* = 503)	*p* value
Sex			
Male (n, %)	98 (49.3%)	244 (48.5%)	0.98
Female (n, %)	104 (51.2%)	258 (51.3%)	0.98
Age (years)	81 [72–85]	81 [72–86]	0.98
Clinical signs			
Orthopnoea (n, %)	177 (87.2%)	32 (6.4%)	< 0.001
Bilateral crackles (n, %)	189 (93.1%)	133 (26.4%)	< 0.001
Bilateral rhonchi (n, %)	27 (13.3%)	100 (19.9%)	0.039
Venous jugular distension (423 pts – n, %)	34 (27.2%)	30 (10.1%)	0.010
Lower-extremity oedema (626 pts – n, %)	97 (52.7%)	158 (35.7%)	0.008
Comorbidities			
Arterial hypertension (n, %)	167 (82.3%)	354 (70.4%)	0.001
Cardiac valvular disease (n, %)	56 (30.0%)	62 (13.0%)	< 0.001
Coronary artery disease (n, %)	73 (36.0%)	124 (24.7%)	0.001
Basal left ventricular EF (%)*	49 [38–57]	55 [44–60]	< 0.001
COPD (n, %)	50 (24.6%)	170 (33.8%)	0.018
Chronic respiratory failure (n, %)	24 (11.8%)	102 (20.3%)	0.011
Chronic renal failure (n, %)	50 (24.6%)	85 (16.9%)	0.019
Diabetes mellitus (n, %)	71 (35.0%)	158 (31.4%)	> 0.05
Chronic medications			
Anticoagulants (n, %)	57 (28.1%)	125 (25.0%)	> 0.05
Antiplatelets (n, %)	104 (51.2%)	186 (37.0%)	< 0.001
Antihypertensives (n, %)	161 (79.3%)	332 (66.0%)	0.001
Diuretics (n, %)	113 (55.7%)	240 (47.7%)	> 0.05
Nitrate (n, %)	34 (16.7%)	68 (13.5%)	> 0.05
Anti-arrhythmics (n, %)	39 (19.2%)	79 (15.7%)	> 0.05
Bronchodilators (n, %)	39 (19.2%)	122 (24.3%)	> 0.05
Oxygen (n, %)	27 (13.3%)	107 (21.3%)[b]	0.013
CPAP (n, %)	4 (2.0%)	7 (1.4%)	> 0.05
NIV (n, %)	2 (1.0%)	2 (0.4%)	> 0.05
Antidiabetics (n, %)	59 (29.1%)	138 (27.4%)	> 0.05
Chronic haemodialysis (n, %)	4 (2.0%)	4 (0.8%)	> 0.05

Percentages refer to each group (HPO and non-HPO)

COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; EF: ejection fraction; HPO: hydrostatic pulmonary oedema; NIV: non-invasive ventilation. * data available for 324 patients (113 HPO, 211 Non-HPO)

(-8.2 [-11.2 to -5.6] vs. 0.6 [-2.1–3.3]%, respectively) and absolute (-1.0 [-1.4 to -0.8] vs. 0.1 [-0.3–0.4]g/dL, respectively) values ($p<0.001$ for both) (Fig. 1; Table 3). The last value of Hb recorded before hospital discharge was not different between HPO and non-HPO patients (11.6 [10.3–13.1] vs. 11.4 [10.2–13.0]g/dL, respectively; $p=0.371$).

Diagnostic ability of ΔHbT1-T0 to detect HPO

Hb value at T_0 detected HPO with an AUROC of 0.591 [0.545–0.636], with a sensitivity of 57 [50–64]% and a sensibility of 58 [54–67]% (Supplementary material 5). A relative ΔHb_{T1-T0} of -5% could detect HPO with a sensitivity of 88 [82–92]% and a specificity of 87 [84–90]%, with an AUROC of 0.901 [0.896–0.906] (Fig. 2, Supplementary material 5). An absolute ΔHb_{T1-T0} of -0.6 g/dL detected HPO with a sensitivity of 85 [83–86]% and a specificity of 89 [88–90]%, with an AUROC of 0.903 [0.897–0.908] (Supplementary material 5). No significant differences emerged when relative and absolute ΔHb_{T1-T0} AUROC curves were compared ($p=0.765$), whereas both curves were superior to the one of Hb at T_0 ($p<0.001$).

Predictive model

With the machine learning approach, the performance of the considered models was similar except for the RPART algorithm, which demonstrated a lower performance, especially in comparison with GBM, which emerged as the best performing algorithm (Supplementary Material 6). The GBM algorithm detected HPO with an AUROC of 0.911 [0.909–0.914]) (Supplementary Material 7). According to the variable importance plot, ΔHb_{T1-T0} was confirmed as the most important covariate for detecting HPO. The predictive tool has been made freely available in a Shiny-web application [24] (Supplementary Material 8).

Table 2 Haemodynamic, biological and ultrasound findings

	HPO (*n* = 203)	Non-HPO (*n* = 503)	*p* value
SAP (mmHg)	147 [125–165]	135 [117–155]	< 0.001
DAP (mmHg)	80 [65–94]	75 [60–85]	< 0.001
HR (bpm)	95 [80–113]	95 [80–110]	> 0.05
RR (breaths/min)	30 [25–38]	28 [22–35]	> 0.05
Body temperature (°C)	36.3 [36.0–36.8]	36.5 [36.0–37.4]	> 0.05
SpO_2 (%)	88 [82–94]	89 [83–93]	> 0.05
PaO_2/FiO_2	232 [187–269]	239 [200–274]	> 0.05
Chest X-ray	197 (98%)	481 (97%)	
Pleural effusion (n, %)	85 (41.9%)	171 (34.0%)	0.048
Lung consolidation (n, %)	30 (14.8%)	136 (27.0%)	< 0.001
Venous stasis (n, %)	197 (97.0%)	112 (22.3%)	< 0.001
Lung ultrasound (n, %)	74 (36.5%)	96 (19.1%)	
Pleural effusion (n, %)	27 (13.3%)	34 (6.7%)	0.005
Lung consolidation (n, %)	4 (2.0%)	12 (2.4%)	> 0.05
B-lines (n, %)	74 (36.5%)	42 (8.3%)	< 0.001
Echocardiography (n, %)*	61 (30.0%)	61 (12.1%)	
Left ventricular EF (%)	36 [30–46]	50 [40–57]	< 0.001

Percentages refer to each group (HPO and Non-HPO)

COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; DAP: diastolic arterial pressure; EF: ejection fraction; HPO: hydrostatic pulmonary oedema; HR: heart rate; PaO_2/FiO_2: arterial oxygen partial pressure over inspired oxygen fraction ratio; RR: respiratory rate; SAP: systolic arterial pressure; SpO_2: peripheral oxygen saturation

Table 3 Haemoglobin changes between HPO and non-HPO patients

	HPO (*n* = 203)	Non-HPO (*n* = 503)	
T_0 from ED admission (min)	10 [5–15]	10 [5–15]	> 0.05
T_1-T_0 (hours)	5.5 [4.7–6.0]	5.7 [4.9–6.1]	> 0.05
Hb_{T0}	13.0 [11.6–14.3]	12.2 [10.9–13.7]	< 0.001
Hb_{T1}	11.7 [10.4–13.2]	12.4 [11.0–14.0]	< 0.001
Relative ΔHb_{T1-T0} (%)	-8.2 [-11.2 – -5.6]	0.6 [-2.1–3.3]	< 0.001
Absolute ΔHb_{T1-T0} (g/dL)	-1.0 [-1.4 – -0.8]	0.1 [-0.3 – 0.4]	< 0.001

Hb_{T0}: haemoglobin at baseline; Hb_{T1}: haemoglobin at T1; ΔHb_{T1-T0}: haemoglobin difference between T1 and baseline; HPO: hydrostatic pulmonary oedema

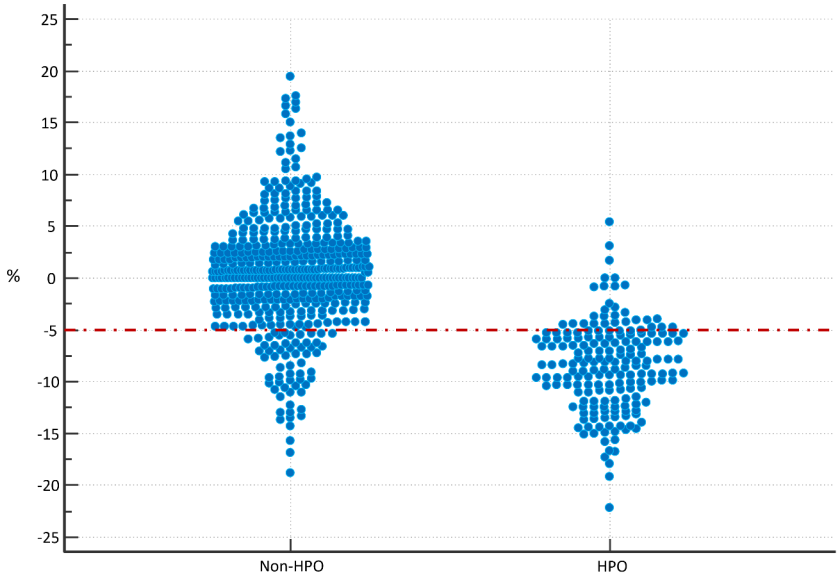

Fig. 1 Percentage haemoglobin changes in HPO and non-HPO patients

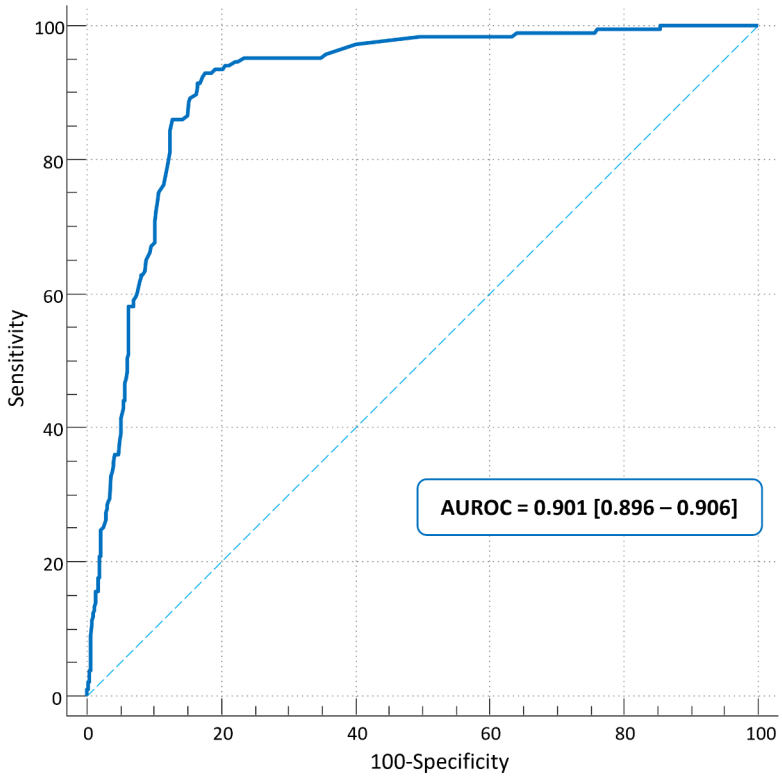

Fig. 2 Area under the receiver operating characteristic curve for the ability of relative ΔHbT1-T0 to detect HPO. AUROC: are under the ROC curve; HPO: hydrostatic pulmonary oedema; ROC: receiver operating characteristics; ΔHb_{T1-T0}: haemoglobin difference between T_1 and baseline

Discussion

Our study shows that a decrease in blood Hb concentration≥5% 4 to 8 h after ED admission compared to the measurement made at the first blood sample reliably detects HPO in patients with dyspnoea. Through a machine learning approach, we could integrate such an information to create a predictive model for improving the role of ΔHb in confirming HPO at 4 to 8 h.

Acute hydrostatic pulmonary oedema results from the increase in pulmonary capillary pressure promoting the filtration of hypo-oncotic fluid from the vessels to the interstitial and alveolar spaces of the lung parenchyma [16]. The most important symptom, which usually brings the patient to seek medical attention at the ED is dyspnoea and is often associated with clinical signs of venous congestion. As for the radiological clues, chest X-ray, CT-scan and lung ultrasounds provide specific findings that are suggestive for HPO [9, 25–27]. Nevertheless, none of these findings is sufficient to diagnose pulmonary oedema [6, 28], alone or combined, to create diagnostic scores [29–31], the overall accuracy is only intermediate and not tailored for the emergency department setting [32–34]. In theory, the direct demonstration of an increased pulmonary artery occlusion pressure would be the reference method for defining HPO as the cause of dyspnoea [19], but right heart catheterisation is most often impossible in the ED [35]. Bedside echocardiography may provide significant information regarding the ventricular function and surrogate estimates of LV filling pressure [36]. Nevertheless, it requires specific skills, it is time consuming and often difficult to perform in patients with respiratory distress [21].

BNP and NT-proBNP, cardiac neurohormones secreted by the ventricles and atria in response to pressure overload, have been shown to have good diagnostic accuracy for HPO. They became the most adopted methods for establishing HPO diagnosis in clinical practice [37–39]. Nevertheless, these variables suffer from a large grey zone of values in which their diagnostic ability is reduced [40, 41], and they are influenced by many factors such as age, sex, and renal impairment [42, 43]. In addition, their determination is costly.

Figueras and Weil [17] firstly showed that changes in haematocrit could be used as estimates of plasma volume changes. Subsequently, they observed a significant increase in total plasma protein concentration and plasma colloid osmotic pressure in patients with acute HPO, compared to the reference group [17]. After treatment of HPO, they observed a significant decrease in haematocrit and total protein concentration, as well as

a significant increase in plasma volume, despite the fact that urine output had exceeded fluid intake. The authors attributed these findings to the fact that treatment and resolution of pulmonary oedema lead to a re-expansion of the intravascular volume due to reabsorption of hypo-oncotic fluid from the lungs [17]. Henning and Weil subsequently evaluated the changes in Hb, plasma colloid osmotic pressure and plasma volume in 14 patients treated for acute cardiogenic pulmonary oedema with phentolamine and furosemide [18]. They observed that 4 h after phentolamine administration, Hb levels and plasma colloid osmotic pressure significantly decreased compared to baseline, whereas the mean plasma volume increased. When furosemide was subsequently administered, Hb further decreased, as well as plasma colloid osmotic pressure. Interestingly, even though urinary output exceeded fluid intake, plasma volume further increased, confirming the plausible explanation that it was related to redistribution of the hypo-oncotic fluid that had migrated to the lungs [18].

These seminal findings have been used to identify HPO in different settings. Among them, the increase in plasma protein and haematocrit levels during spontaneous breathing trials in mechanically ventilated patients in the ICU has been shown to reliably identify "weaning-induced pulmonary oedema" (WIPO) as the reason for SBT failure [19–21, 44]. Also, in patients with chronic heart failure, it has been recently shown that changes in Hb are significantly correlated with changes in diastolic pulmonary artery pressure, making haemoconcentration a plausible marker for ambulatory evaluation of clinical stability of such patients [45]. Other studies investigated Hb changes over days specifically in patients admitted for heart failure [46, 47], but none in a general population of dyspnoeic patients at the ED.

Our study demonstrates the solidity of Hb changes in detecting HPO in dyspnoeic patients in the emergency department. At ED presentation, the Hb level were slightly but significantly higher in HPO compared to non-HPO patients. It decreased in HPO patients at T_1, which is in line with the findings of Henning and Weil in HPO patients [18], while it remained unchanged in patients with no HPO. Even more, the relative and absolute ΔHb_{T1-T0} reliably detected HPO, with a large AUROC and high positive predictive values (Supplementary Material 5). This diagnostic accuracy was better than the Hb value measured at T_0. No differences in Hb levels between HPO and non-HPO patients were observed before hospital discharge. Interestingly, the diagnostic threshold of Hb changes we found for HPO detection is similar to the one observed by Dres et al. for the diagnosis of WIPO [20].

As a clinical application, our results suggest that considering the changes in Hb should allow a reliable diagnosis of HPO. We measured Hb level changes between admission and H-4 to H-8, so that the diagnosis could only be retrospective. Even more, the decrease in haemoconcentration would likely not have been observed without an efficient treatment of HPO. Then, the method could not be used to make HPO diagnosis on admission and decide for a therapeutic strategy. However, confirming the diagnosis of HPO *a posteriori* may still have clinical benefit. Moreover, the machine learning approach allowed us to create a predictive model to evaluate how Hb changes influence the likelihood of having HPO after such a time interval, according to other significant elements that a priori could influence the final diagnosis, notably chronic health conditions. In this regard, the GBM model showed an excellent ability for HPO detection through ΔHb_{T1-T0}, which emerged as the most significant covariate that could determine the patient's status. Through the web-based application, such model could be used in clinical practice to confirm the diagnosis. Nevertheless, further studies should investigate whether a shorter-term assessment of the decrease in haemoconcentration would perform with a similar diagnostic accuracy e.g., after only one hour.

Limitations

This study has several limitations. First, this is a retrospective single-centre analysis, and our results should be confirmed in a prospective cohort, on a shorter interval for the second Hb measurement. Second, the diagnosis of HPO was established by two experts, based on several arguments. Indeed, no other solution could have been chosen as the reference, provided that the pulmonary artery catheter cannot be used in the context where we conducted the study. Third, BNP was not available for most of the patients, which may have added a substantial clue for the determination of HPO. Fourth, we did not specifically compare Hb levels variation among patients with an intravascular congestion phenotype and patients with a tissue congestion phenotype (both pulmonary and systemic). Finally, Hb was assessed through the blood gas analyser, and haematocrit and plasma protein concentration were not used to estimate haemoconcentration as done by other authors [19]. However, this is no obvious argument why these variables should indicate haemoconcentration better than Hb.

Conclusion

Decrease in Hb concentration over the first hours of treatment reliably identifies hydrostatic pulmonary oedema as the main cause of dyspnoea in patients admitted to the emergency department.

Abbreviations

BNP	B-type natriuretic peptide
CRP	C-reactive protein

ECG	Electrocardiogram
ED	Emergency department
GBM	Gradient boosting machine
GLMNET	Generalized linear model via elastic net penalized maximum likelihood
Hb	Haemoglobin
HPO	Hydrostatic pulmonary oedema
ICU	Intensive care unit
LVEF	Left ventricular ejection fraction
RF	Random forest
RPART	Recursive partitioning and regression trees
SBT	Spontaneous breathing trial
SVM	Support vector machine
WIPO	Weaning-induced pulmonary oedema
T_0	ED admission
T_1	4 to 8 h from ED presentation
ΔHb_{T1-T0}	The difference between Hb values between T_1 and T_0

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12245-024-00698-y.

Supplementary Material 1

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This study was presented at the 36th annual congress of the European Society of Intensive Care Medicine (21– 25 October 2023, Milan, Italy) and awarded as one of the ten best abstracts of the congress.

Author contributions
FG conceived and designed the study, performed data analysis and interpretation, and wrote the manuscript. LMC and DA performed data analysis and interpretation and contributed to writing the manuscript. XM, JLT and GCA participated in data analysis and interpretation and contributed to writing the manuscript. IN, SP, VGV, MaBer, CF, MiBel acquired the data and contributed to data analysis. MaBel, PPS, NDV, FP participated in data interpretation and contributed to writing the manuscript. All authors reviewed and approved the manuscript.

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Data availability
The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Local Ethic Committee (Comitato Etico Territoriale Interaziendale AOU Maggiore della Carità di Novara, CE 93/20). Due to the retrospective nature of the study, the Ethic Committee considered the need for an informed consent as not necessary. The authors certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
Xavier MONNET and Jean-Louis TEBOUL are members of the Medical Advisory Board of Pulsion Medical Systems (Getinge). Xavier MONNET gave lectures for Baxter Healthcare and AOP. The other authors have no conflicts of interest to declare.

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