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ABSTRACT

Background: Literature suggests that Hyperventilation Syndrome (HVS) should be diagnosed and treated pre-hospitally.

Aim: To determine diagnostic accuracy for HVS of paramedics and emergency medical technicians using hospital doctors' diagnosis as the reference standard.

Methods: A retrospective audit of routine data utilising linked pre-hospital and in-hospital patient records of adult patients (≥ 18 years) transported via emergency ambulance to two Emergency Departments in the United Kingdom from 01/01/2012–31/12/2013. Accuracy was measured using sensitivity, specificity, predictive values and likelihood ratios with 95% confidence intervals.

Results: A total of 19386 records were included in the analysis. Pre-hospital clinicians had a sensitivity 88% (95% CI 82-92%) and specificity 99% (95% CI 99-99%) for diagnosing HVS, with PPV 0.42 (0.37, 0.47), NPV 1.00 (1.00, 1.00), LR+ 75.2 (65.3, 86.5) and LR- 0.12 (0.08, 0.18).

Conclusions: Paramedics and emergency medical technicians were able to diagnose HVS pre-hospitally with almost perfect specificity and good sensitivity.

Abstract Word Count: 150 words

KEY WORDS

Sensitivity and Specificity; Hyperventilation Syndrome; Panic attack; Emergency Medical Services; Diagnostic Accuracy; Clinical Diagnosis

KEY POINTS

- Paramedics and emergency medical technicians were able to diagnose HVS pre-hospitally with almost perfect specificity and good sensitivity.
- Pre-hospital diagnosis of HVS is most accurate in patients less than 30 years of age.
- Uncertainty in HVS as sole diagnosis should be a red flag for non-conveyance.
- Future research should address further evidence gaps in diagnosing HVS such as the roles of previous HVS episodes and end-tidal carbon dioxide, as well as qualitative research addressing the decision-making process and the element of uncertainty surrounding HVS diagnosis.

REFLECTIVE QUESTIONS

- What are your local policies in regards to referring a patient with HVS? If none exist then check the JRCALC 2019 guidance on Hyperventilation Syndrome.
- Reflect upon your own decision-making process when diagnosing a patient with HVS
- What are your thoughts on pre-hospital clinicians misclassifying 12% of patients as suffering with HVS when they did not have HVS?

ARTICLE WORD COUNT

2955 words

TITLE

Pre-Hospital Diagnostic Accuracy for Hyperventilation Syndrome – A Diagnostic Study

INTRODUCTION

Hyperventilation syndrome (HVS) has been used for almost a century to describe "a collection of physical and biochemical reactions from an unnecessarily increased respiratory rate that occurs due to an unknown or benign aetiology, which can be triggered by anxiety in the absence of other external factors[1,p.45]. It encompasses a wide variety of symptoms and is diagnosed by excluding organic causes for patients' symptoms[2]. Despite the difficulty surrounding HVS diagnosis and particularly the lack of HVS decision-making tools for pre-hospital clinicians, literature suggests that HVS should be diagnosed and treated pre-hospitally to avoid costly attendances at Accident and Emergency (A&E) departments[3].

The aim of this diagnostic research study was to measure how accurately paramedics and Emergency Medical Technicians (EMTs) in the pre-hospital setting diagnosed HVS.

The objectives were:

- To describe the characteristics of patients diagnosed with HVS
- To identify diagnostic tests and therapeutic interventions performed pre-hospitally and in A&E for HVS patients
- To estimate the pre-hospital diagnostic accuracy for HVS as measured through sensitivity and specificity

METHODS

The study encompassed a consecutive series of patients similar to a cohort study, which corresponds to a single-gate diagnostic accuracy study design[4]. A retrospective approach of

reviewing patients' hospital notes and pre-hospital electronic Patient Report Forms (ePRFs) was decided upon because it provided a more accurate reflection of clinical practice and enabled the inclusion of a larger sample size.

Study Population

Records of patients were included if patients were ≥ 18 years old and transported by the regional emergency ambulance service to the A&E departments of two neighbouring UK hospitals between 01/01/2012-31/12/2013. Exclusion criteria were private transport, direct admission to a hospital ward, inter-facility transfers and paper pre-hospital records.

Index Test and Reference Standard

The chosen index test was the diagnosis given to patients by pre-hospital clinicians documented in the EPRF's impression tick-box or free-text. The chosen reference standard was the diagnosis given to patients by A&E doctors as documented within patients' medical notes. The reference standard was selected because it was deemed to be the closest option to the hypothetical gold standard answer providing full certainty of whether a patient was presenting with HVS[5].

Blinding

Local protocols required pre-hospital clinicians to have finalised their ePRFs prior to patients being assessed in-hospital, which means they should not have been unaware of patients' in-hospital diagnosis when making their initial diagnosis. Although this sequence of events suggests that pre-hospital clinicians were blinded to the reference standard, the retrospective nature of this study did not allow for inclusion of a confidence procedure to ensure compliance with the requirement to finalise ePRFs in a timely fashion so we cannot report that blinding occurred. Hospital physicians will have likely consulted pre-hospital ePRFs and will have

therefore been aware of the proposed pre-hospital diagnosis, meaning that they were not blinded.

Data was collected utilising separate data collection forms in two distinct phases to ensure that the researcher was blind to the patients' index test or reference standard results whilst collecting data thereby reducing the risk of test review bias and diagnostic review bias[6;7].

Data Analysis

Descriptive data was reported as number (percent) for categorical variables and mean (standard deviation) for metric variables with normal distribution or median (minimum-maximum) with skewed distribution[8;9].

To estimate diagnostic accuracy, sensitivity and specificity were measured, as well as Positive/Negative Predictive Values (PPV/NPV) and Positive/Negative Likelihood Ratios (LR+/LR-) calculated using the Stata command 'diagt'[10]. Likelihood ratios were depicted visually using a Fagan nomogram[11]. Corresponding 95% Confidence Intervals (CI) were calculated to analyse the variability associated with each estimate[12].

The percentage and index test results of missing data were reported and a sensitivity analysis planned to explore whether diagnostic accuracy estimates would be altered if patients with missing data were assumed to be false negatives or false positives[13].

Several subgroup analyses were planned in advance to avoid introducing bias through post-hoc analyses. Statistically, these subgroup analyses were conducted using Chi^2 tests or Fisher's exact test. Results were deemed statistically significant at the 0.05 level, if p-values were below p=0.05/8=0.00625. This modified p-value was obtained using a Bonferroni correction to address the increased possibility of false positive results associated with multiple hypothesis testing[14].

Sample Size

Due to not knowing what sensitivity and specificity values to anticipate, it was not possible to conduct a formal sample size calculation. For pragmatic reasons a sample of two years from 2012-2013 was decided upon due to ePRFs subsequently being discontinued by the ambulance service in this locality.

Ethical Considerations

To identify eligible patient records, two gatekeepers were appointed to identify and anonymise the records of HVS patients within their hospital/ambulance trust, which they matched using a pseudonymisation code in a process known as data linkage[15]. Summarised information on the patients not diagnosed with HVS in either setting was obtained in anonymised form through the ambulance services' clinical governance department as less in-depth data was required for these patients.

Using the above described principles of data collection, the study was exempt from obtaining informed consent because the researcher only had access to data after it had been processed by the gatekeepers and therefore did not view or collect patient-identifiable information. Furthermore, the principle of confidentiality was observed because re-identification of patients was not possible and the data was considered "de-identified information"[16,p.88]. This resulted in a favourable ethical opinion from the University of Leeds School of Healthcare ethics committee (HREC15-021).

RESULTS AND ANALYSIS

As illustrated in Figure 1, a total of 19393 patient records were eligible for the study. Of these, 7 were excluded due to patient records being irretrievable (n=4) and patients leaving A&E prior to being assessed (n=3). Patient records fell into one of four categories:

- True positive: patients diagnosed with HVS in the pre-hospital and hospital setting
- False positive: patients diagnosed with HVS pre-hospitally but not in hospital
- False negative: patients diagnosed in hospital with HVS but not pre-hospitally
- True negatives: patients not diagnosed with HVS in pre-hospital or hospital setting

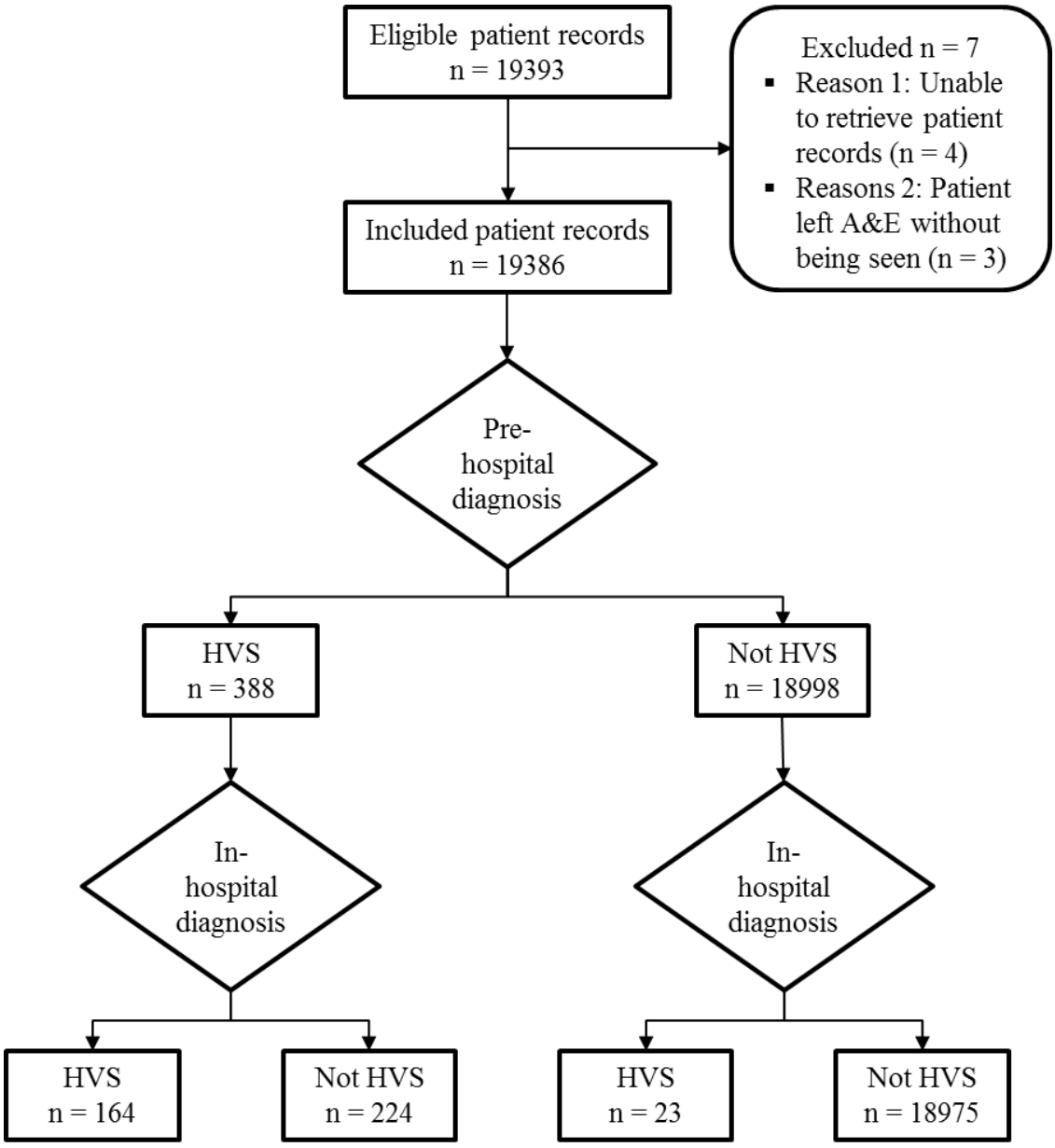


Figure 1: Diagram Reporting Flow of Participants through the Study

Study Population

The median age of the 19386 study patients was 58 years. The median age was 48 years for patients diagnosed with HVS pre-hospitally and 32 years for patients diagnosed with HVS in hospital (Table 1). There was unequal representation of male and females within the study sample, with females being more prevalent in all four categories at a statistically significant level (p=.014).

Referral to the onsite Primary Care Centre was most frequent for patients diagnosed in hospital with HVS. In contrast, being admitted to a hospital ward was most common in false positive patients. Length of median stay was longer for false positive patients than for true positive patients. Rates of re-attendance to the A&E department within 28 days were similarly high across the groups. In-hospital mortality was noted for two false positive patients with in-hospital diagnoses of chronic obstructive pulmonary disease and pulmonary embolism, following hospital admissions for 4 and 5 days respectively.

Table 1: Baseline Demographic Details and Patient Outcomes for the Study Cohort

VARIABLE/ CATEGORIES		TOTAL SAMPLE (N = 19386)	TRUE POSITIVE (N = 164)	FALSE POSITIVE (N = 224)	FALSE NEGATIVE (N = 23)
Median Age in Years		58	32 (18-93)	48 (18-95)	32 (18-92)
Sex	Male	8673 (44.74%)	57 (34.76%)	92 (41.07%)	12 (52.17%)
	Female	10251 (52.88%)	107 (65.24%)	132 (58.93%)	11 (47.83%)
	Missing	462 (2.38%)	-	-	-
Referred to Primary Care Centre		-	30 (18.29%)	8 (3.57%)	6 (26.09%)
Admitted to Hospital Ward		-	5 (3.05%)	85 (37.95%)	0 (0)
Length of Stay in Days		-	2 (2-9)	3 (1-21)	0
A&E Re-Attendance within 28 Days		-	32 (19.51%)	48 (21.43%)	6 (26.09%)

In-Hospital Mortality	-	0 (0)	2 (0.89%)	0 (0)

Patient Characteristics

Overall, patients diagnosed with HVS presented most often with tachypnoea, feeling anxious, chest pain and shortness of breath, as well as past medical problems of anxiety, mental health problems and respiratory disorders (Table 2). Vital signs were similar across the groups and at the high end of normal adult pre-hospital limits.

Table 2: Clinical Characteristics for HVS Patients in the Study

VARIABLE	CATEGORIES	TRUE POSITIVE (N = 164)	FALSE POSITIVE (N = 224)	FALSE NEGATIVE (N = 23)
Signs and Symptoms	Tachypnoea	124 (75.61%)	119 (53.13%)	14 (60.87%)
	Fear, feeling anxious	75 (45.73%)	77 (34.38%)	12 (52.17%)
	Chest pain	56 (34.15%)	117 (52.23%)	4 (17.39%)
	Shortness of breath	54 (32.93%)	94 (41.96%)	8 (34.78%)
	Paraesthesia to limbs/face	45 (27.44%)	18 (8.04%)	5 (21.74%)
	Dizziness	39 (23.78%)	58 (25.89%)	9 (39.13%)
	Palpitations	10 (6.10%)	13 (5.80%)	1 (4.35%)
	Feeling confused or unreal	4 (2.44%)	0 (0)	1 (4.35%)
	Blurred vision	3 (1.83%)	3 (1.34)	0 (0)
Past Medical History	HVS, anxiety/panic disorders or attacks	99 (60.37%)	77 (34.38%)	8 (34.78%)
	Other mental health problems	49 (29.88%)	62 (27.68%)	6 (26.09%)
	Respiratory i.e. asthma, chronic obstructive pulmonary disease, pneumothorax or pulmonary oedema	31 (18.90%)	75 (33.48%)	5 (21.74%)
	Cardiac i.e. MI, angina or arrhythmia	11 (6.71%)	37 (16.52%)	3 (13.04%)
	Neurological i.e. stroke, transient	4 (2.44%)	20 (8.93%)	2 (8.70%)

	ischaemic attack or epilepsy			
	Pulmonary embolism or deep vein thrombosis	2 (1.22%)	2 (0.89%)	0 (0)
	Diabetes	2 (1.22%)	17 (7.59%)	3 (13.04%)
Vital Signs	RR/min	21 (9)	20 (6)	22 (16)
	HR/min	95 (19)	92 (19)	92 (20)
	SpO_2 %	99 (1)	97 (4)	98 (2)
	Pain	1 (2)	3 (3)	1 (2)
	PHEWS	2 (2)	2 (2)	2 (2)
	PHEWS red box	27 (16.46%)	29 (12.95%)	3 (13.04%)

For the 224 false positive patients, the most frequent hospital diagnoses were non-cardiac chest pain, acute coronary syndrome, chronic obstructive pulmonary disease and chest infection; whereby, only 3 were diagnosed with a pulmonary embolism (Table 3). For the 23 false negative patients, common alternative pre-hospital diagnoses were other medical problem, other mental health problem and unknown problem, which indicated the difficulty and uncertainty surrounding patients' assessment and diagnosis.

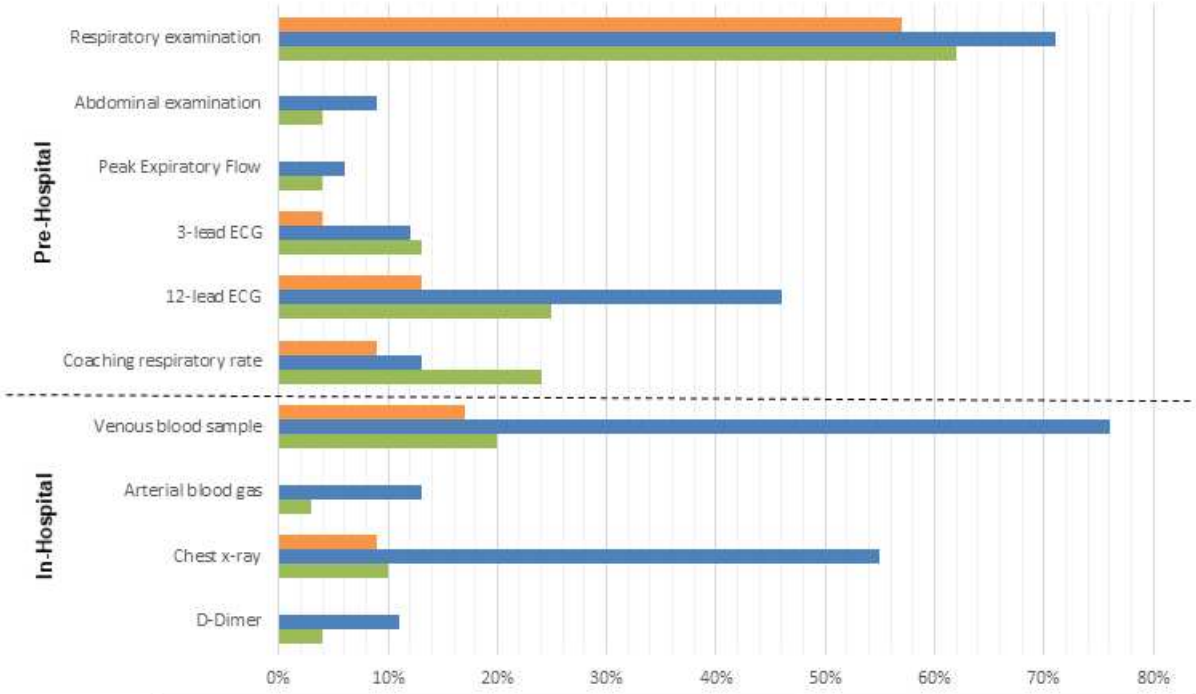
Table 3: Alternative Diagnosis for False Positive and False Negative Patients

PATIENT GROUP	DIAGNOSIS	TOTAL NUMBER	PERCENT
False Positive (n = 224)	Non-cardiac chest pain	52	23.21%
	Acute coronary syndrome	33	14.73%
	Chronic obstructive pulmonary disease	21	9.38%
	Chest infection or pneumonia	19	8.48%
	Other medical problem	12	5.36%
	Acute abdominal pain	11	4.91%
	Mental health problem	11	4.91%
	Minor injuries	10	4.46%
	Other cardiac diagnoses	9	4.02%
	Other gastrointestinal diagnoses	9	4.02%
	Asthma	8	3.57%
	Collapse or non-epileptic fit	8	3.57%
	Other respiratory diagnoses	7	3.13%

	Alcohol or drug related problem	7	3.13%
	Other neurological diagnoses	3	1.34%
	Pulmonary embolism	3	1.34%
	No acute medical problem	1	0.45%
False Negative (n = 23)	Other medical problem	13	56.52%
	Other mental health problem	3	13.04%
	Unknown problem	2	8.70%
	Asthma	1	4.35%
	Dementia	1	4.35%
	Faint	1	4.35%
	Other neurological problem	1	4.35%
	Other respiratory problem	1	4.35%

Clinical Assessments

Clinical assessments consisted of pre-hospital and in-hospital examinations and diagnostic tests that were conducted as part of routine practice but none were exclusive to diagnosing HVS (Figure 2). Pre-hospitally, respiratory examinations were most commonly conducted. There was evidence in patients' records that almost a quarter of true positive patients received coaching on their breathing, which was less prevalent amongst misdiagnosed patients. In hospital, patients diagnosed with HVS received fewer assessments compared with false positive patients. However, overall obtaining venous blood samples and performing chest x-rays were most frequent.



	Pre-Hospital						In-Hospital			
	Respiratory examination	Abdominal examination	Peak Expiratory Flow	3-lead ECG	12-lead ECG	Coaching respiratory rate	Venous blood sample	Arterial blood gas	Chest x-ray	D-Dimer
False negative	13 (57%)	0	0	1 (4%)	3 (13%)	2 (9%)	4 (17%)	0	2 (9%)	0
False positive	158 (71%)	20 (9%)	13 (6%)	26 (12%)	103 (46%)	30 (13%)	171 (76%)	29 (13%)	124 (55%)	24 (11%)
True positive	102 (62%)	6 (4%)	6 (4%)	22 (13%)	41 (25%)	39 (24%)	32 (20%)	5 (3%)	17 (10%)	6 (4%)

Figure 2: Clinical Assessments for HVS Patients in the Study

Estimation of Diagnostic Accuracy

		Hospital diagnosis of HVS		
		Yes	**No**	
Pre-hospital diagnosis of HVS	**Yes**	**164** True positive	**224** False positive	234
	No	False negative **23**	True negative **18975**	18998
		187	19199	= 19386

Figure 3: Cross Tabulation of Index Test Results by Reference Standard Results

Overall, pre-hospital clinicians' diagnosis of HVS had a sensitivity 88% (95% CI 82-92%) and specificity 99% (95% CI 99-99%) (Figure 3). This means, pre-hospital clinicians identified correctly 88% of individuals who had HVS and correctly identified 99% of patients not suffering with HVS.

The calculated predictive values were PPV 0.42 (0.37, 0.47) and NPV 1.00 (1.00, 1.00). The NPV shows that if pre-hospital clinicians diagnosed patients as not having HVS, they were 100% likely not to be diagnosed with HVS in hospital. Although, this value suggests absolute certainty, it should be noted that this measurement was subject to rounding and that a small number of study patients were diagnosed with HVS in hospital after not being diagnosed with HVS pre-hospitally. The PPV demonstrated that patients diagnosed with HVS pre-hospitally had a chance of 42% of being diagnosed with HVS in hospital.

Likelihood ratios were 75.2 (65.3, 86.5) for a positive diagnosis and 0.12 (0.08, 0.18) for a negative diagnosis. The likelihood ratios were combined visually with prevalence of HVS in the study population (pr=0.96%) in a Fagan nomogram (Figure 4). The graph illustrated that prior to being assessed pre-hospitally, patients had a pre-test probability of 0.96% of being diagnosed with HVS in hospital. However, if a pre-hospital clinician diagnosed a patient with HVS then this probability increased to 39%. If a pre-hospital clinician deemed a patient to not be suffering with HVS then this probability decreased to close to 0%.

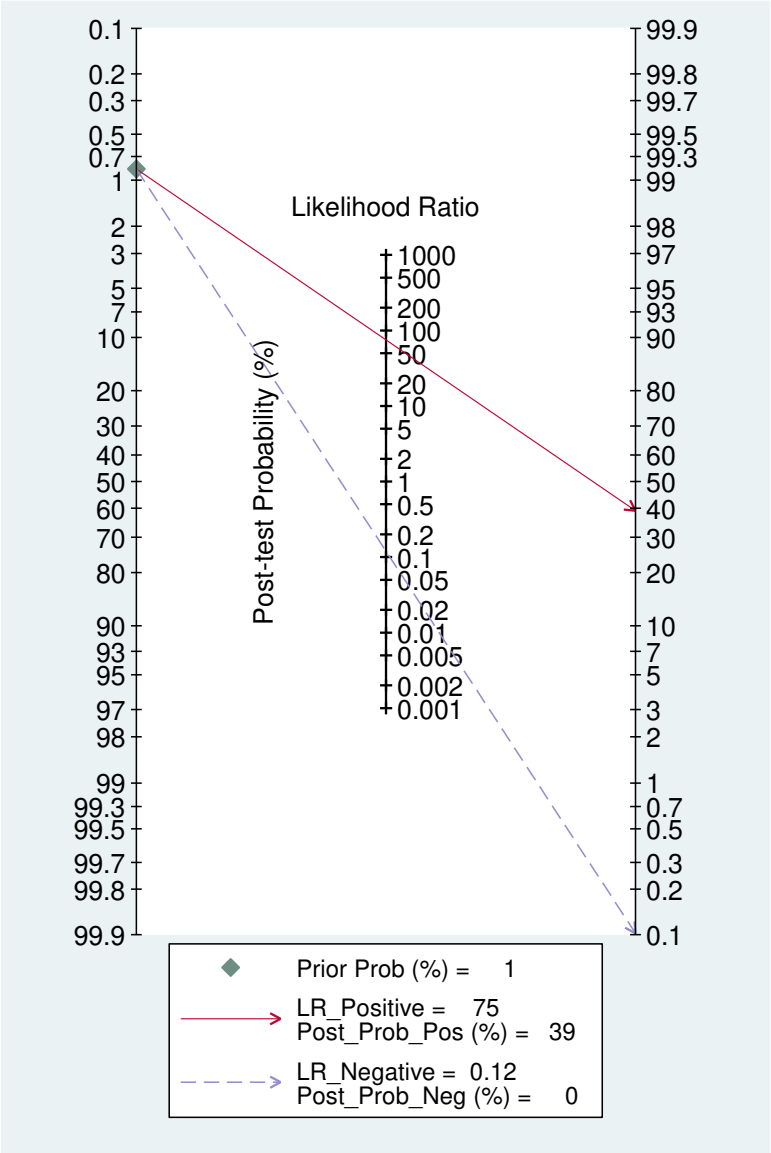


Figure 4: Fagan's Bayesian Nomogram

Subgroup Analyses

The study sample size was too small to draw statistically significant conclusions regarding whether sensitivity varied according to the number of pre-hospital diagnoses, pre-hospital clinician qualification, patient age or patient sex (Table 4). Furthermore, it was not possible to determine specificity or NPVs across subgroups due to diagnosis information being unavailable for true negative patients. However, a statistically significant difference ($p<0.001$) was evident for PPV depending on the number of pre-hospital diagnoses and patient age. If a pre-hospital clinician solely selected a diagnosis of HVS then the patient had a probability of 80% of being diagnosed with HVS in hospital; however, if two or more diagnoses were documented, then the patient's probability of being diagnosed with HVS in hospital was 20%. Overall, the probability that patients diagnosed with HVS pre-hospitally were diagnosed with HVS in hospital decreased with increasing patient age with the exception of patients aged ≥70.

Table 4: HVS Study Subgroup Analyses Results

VARIABLE	CATEGORIES	SENSITIVITY	P-VALUE	POSITIVE PREDICTIVE VALUE	P-VALUE
Number of Pre-hospital Diagnoses	1	0.87 (0.80, 0.92)	0.488	0.80 (0.72, 0.86)	< 0.001
	≥ 2	0.90 (0.79, 0.97)		0.20 (0.15, 0.25)	
Pre-hospital clinician qualification	Paramedic	0.87 (0.81, 0.92)	0.477	0.42 (0.37, 0.48)	0.954
	EMT-II	0.95 (0.74, 1.00)		0.42 (0.27, 0.58)	
Patient Age	< 30	0.87 (0.79, 0.94)	1.000	0.64 (0.55, 0.73)	< 0.001
	30-40	0.86 (0.65, 0.97)		0.37 (0.24,0.52)	
	40-50	0.96 (0.80, 1.00)		0.36 (0.25, 0.49)	

	50-60	0.88 (0.64, 0.99)		0.33 (0.20, 0.48)	
	60 - 70	0.93 (0.68, 1.00)		0.28 (0.16, 0.43)	
	≥ 70	0.76 (0.53, 0.92)		0.29 (0.17, 0.42)	
Patient Sex	Male	0.83 (0.72, 0.92)	0.105	0.38 (0.30, 0.47)	0.206
	Female	0.91 (0.84, 0.95)		0.45 (0.38, 0.51)	

Missing Data

As previously indicated, data was missing for 7 patients, which was 0.00036% of the total sample size. Conducting the pre-planned sensitivity analysis meant a decrease in sensitivity of 0.005 and a decrease in specificity of 0.0003, which was considered to be very small and not clinically relevant.

DISCUSSION

Patient Demographics and Outcomes

The study prevalence of HVS (pr=0.96%) was similar to the 0.3% found by Pfortmueller et al.[2] but considerably lower than the 6-11% cited in other literature[17-21]. However, the higher prevalence was determined in patients with respiratory, cardiac and gastrointestinal problems and has been criticised as not accurately representing the wider population[22].

Patients who had an in-hospital diagnosis of HVS were on average 26 years younger than study patients overall, which reflects findings by Pfortmueller et al.[3] and Brashear[23] that HVS is most common between 20-40 years of age. Pre-hospitally, HVS was diagnosed 1.6 times as often in women than in men, which is slightly less than the 2-4 reported in the literature[17;24]; although, equal sex incidence was reported by Saisch et al.[25] and Lum[26].

Rates of hospital admission, length of stay and mortality for patients diagnosed in hospital with HVS were comparable to those found by Pfortmueller et al.[3] and support that HVS is not a life-threatening condition[27;28]. The two cases of mortality were false positives, who had HVS recorded as one of numerous pre-hospital diagnoses and were treated pre-hospitally with oxygen-driven nebulisers. This suggests that paramedics were not convinced of the proposed HVS diagnoses as oxygen or nebuliser therapy are not indicated for HVS[29].

Referrals to the Primary Care Centre were made for almost a fifth of HVS patients, which is a new finding not previously examined in the literature. However, this is supported by suggestions in the wider literature that invasive procedures and emergency treatments are not routinely required for HVS patients[27;28].

Re-admission rates (19-26%) were considerably higher than the 0.5% reported by Pfortmueller et al.[2], which suggests A&E diagnoses were potentially incorrect or that HVS patients were frequent A&E attenders in line with suggestions by Harvison et al.[30].

Clinical Characteristics, Past Medical History and Vital Signs

Tachypnoea was the most common sign observed in study patients, which is appropriate given that HVS is defined as "breathing in excess of metabolic requirements"[31,p.7]. Chest pain was the most commonly reported symptom by false positives, which mirrors reports in the wider literature[18;19;32]. However, chest pain was reported much less by true positives and false negatives, which supports Gardner's[33] hypothesis that chest tightness is not a symptom of HVS. Breathlessness, dizziness and paraesthesia were reported in the study to a lesser extent than in the wider literature[3;18;19;21;24]. The variation in HVS symptoms between the study and the wider literature illustrated the highly variable frequency of HVS symptoms and the difficulty of diagnosing HVS[18-20].

On average patients' vital signs were within normal adult pre-hospital limits but 13-16% of patients had observations which were outside acceptable parameters and triggered early warning scores. Although, triggers were equally spread across the groups they indicated different things: critical underlying pathology for false positives and unresolved idiopathic hyperventilation episodes for true positives and false negatives. However, for pre-hospital clinicians these indications were unclear when making a diagnosis; thereby, emphasizing that patients should only be considered for non-conveyance if symptoms have resolved[29].

Differential Diagnoses

Of the most common diagnoses proposed in hospital only acute coronary syndrome required emergency treatment; although, it could be argued that non-cardiac chest pain required invasive diagnostic tests. Other diagnoses such as chronic obstructive pulmonary disease and chest infections can often be treated by primary care services[34;35]. In fact, referrals to specialist community teams are encouraged in an effort to reduce hospital admissions for patients with chronic conditions[36]. Therefore, even for false positives, transport to A&E may not necessarily be in patients' best interest.

Clinical Assessments

The performed clinical assessments illustrated clinicians' attempts to exclude differential diagnoses using physical examinations and diagnostic tests, which were also found in the wider literature[28;30;37]. An example was 12-lead ECGs which were performed almost twice as often in false positives than in true positives. This could indicate that paramedics were unsure about their proposed HVS diagnosis and were conducting further tests to investigate cardiac differential diagnoses.

Diagnostic Accuracy of Pre-Hospital Clinicians

The sensitivity 88% (95% CI 82-92%) and specificity 99% (95% CI 99-99%) of pre-hospital clinicians' diagnosis of HVS were slightly higher than the pooled estimate obtained in a meta-analysis on pre-hospital diagnostic accuracy by Wilson et al.[38]. This means that pre-hospital clinicians were better at correctly identifying patients with HVS and without HVS on average than conditions studied in other pre-hospital diagnostic accuracy studies.

Similar to findings in the review by Wilson et al.[38], this study found higher specificity than sensitivity, i.e. prehospital clinicians were better at excluding HVS than they were at recognising HVS. This issue is somewhat over-emphasized by the PPV, which indicates that 58% of patients diagnosed with HVS pre-hospitally were subsequently not diagnosed with HVS in hospital. However, the PPV is strongly influenced by the low prevalence of HVS in this study; therefore, emphasis should be placed on the sensitivity value, which suggests that 12% of patients were misclassified pre-hospitally as having HVS. Clinically, it is concerning that more than 1 in 9 pre-hospital HVS patients were wrongly diagnosed; therefore, pre-hospital HVS guidelines should advocate safety-netting via direct referrals to primary care centres and giving patients appropriate worsening advice.

Limitations

A major limitation was that not all eligible ePRFs were identified due to a fault with the automatic search string. A further source of study limitations was the study's pioneering status, which meant that sample size and subgroup analyses were based on clinical experience rather than existing literature. In addition, only patients transported to A&E with ePRFs were included; therefore, excluding an unknown number of patients who may have refused transport, been discharged or referred by paramedics, or for whom paper records were completed. Lastly, the choice of reference standard could be questioned in light of the unexpectedly high re-

admission rates implying potentially incorrect A&E diagnoses. This could be explored in further prospective research studies measuring hospital doctors' diagnostic accuracy of HVS or simulated pre-hospital studies utilising an alternative reference standard.

Conclusion

In conclusion, it is recommended that pre-hospital clinicians should be entrusted to diagnose HVS and directly refer adult HVS patients to primary care services if patients' symptoms have resolved. However, this recommendation only applies to adult patients as paediatric patients were not enrolled in the current study.

The study's subgroup analysis suggests that a pre-hospital diagnosis of HVS is most accurate in patients less than 30 years of age so pre-hospital clinicians should be made aware that diagnostic accuracy of HVS decreases with increased age and exercise caution when referring patients aged over 30. Furthermore, the subgroup analysis suggests that the accuracy of diagnosing HVS was significantly reduced if two or more impression terms were selected; therefore, uncertainty in HVS as sole diagnosis should be a red flag for non-conveyance.

Future research should address further evidence gaps in diagnosing HVS such as the roles of previous HVS episodes and end-tidal carbon dioxide[29;39;40], as well as qualitative research addressing the decision-making process and the element of uncertainty surrounding HVS diagnosis.

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