ADVANCES

Potential impact of *N*-terminal pro-BNP testing on the emergency department evaluation of acute dyspnea

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SEE ALSO COMMENTARY, PAGE 259.

ABSTRACT

Objectives: Measurement of the serum B-type natriuretic peptide (BNP) level and more recently its precursor, *N*-terminal proBNP (NT-proBNP), has been advocated to facilitate the diagnosis of heart failure in the emergency department (ED). We sought to determine the potential impact of adding NT-proBNP testing to the routine evaluation of emergency patients with acute dyspnea.

Methods: This prospective cohort study enrolled a convenience sample of acutely dyspneic patients at a tertiary care ED. We excluded trauma patients and those under 30 years of age. Patients underwent standard evaluation, including radiography when indicated. At the point of final diagnosis and blinded to the NT-proBNP result, physicians documented the likelihood that heart failure accounted for the patient's acute dyspnea on a 7-point Likert scale, the data from which was subsequently collapsed to 3 categories for analysis purposes. The primary outcome was the agreement between clinical impression and the NT-proBNP assay classified using manufacturer-recommended, age-specific cut-offs. Newly proposed cut-offs from a recent study were also evaluated.

Results: One hundred and twenty-nine patients making 139 ED visits were enrolled (median age 76 years; 59% admitted). The serum NT-proBNP assay was positive in 119 (86%, 95% confidence interval [CI] 80%–91%) cases, including 75% (43/57, 95% CI 62%–86%) of the cases that the treating physician felt were not caused by heart failure, and 86% (25/29, 95% CI 68%–96%) where the treating physician was unsure. The median NT-proBNP concentration was higher in patients clinically believed to have heart failure rather than pneumonia or chronic obstructive pulmonary disease; however, the ranges of these values overlapped extensively (median 4361 pg/mL; interquartile range [IQR] 2386–10877 v. 1651 pg/mL; IQR 370–4745, respectively).

Conclusions: There is high discordance between the clinical impression of treating physicians and NT-proBNP concentrations, notably in patients who are believed not to have heart failure. Although the reference standard of ED diagnosis is imperfect, the broad overlap in NT-proBNP concentrations suggests poor specificity in this target patient population. The introduction of routine ED NT-proBNP testing using the current cut-offs would be expected to result in substantial indirect costs from further diagnostic testing. It remains unclear whether the introduction of this diagnostic test would have a positive impact on clinically relevant patient outcomes.

Key words: NT-proBNP; natriuretic peptides; heart failure; diagnostic tests

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RÉSUMÉ

Objectifs : On a recommandé le recours au dosage du taux sérique de peptide natriurétique de type B (BNP) et plus récemment, de son précurseur, le fragment *N* terminal du BNP (NT-proBNP), pour faciliter le diagnostic de l'insuffisance cardiaque à l'urgence. Nous avons tenté de déterminer l'impact possible de l'ajout du dosage du NT-proBNP dans le cadre de l'évaluation de routine des patients reçus à l'urgence pour des symptômes de dyspnée aiguë.

Méthodes : Cette étude de cohortes prospective a inclus un échantillon de commodité de patients souffrant de dyspnée aiguë reçus dans un service d'urgence de soins tertiaires. Nous avons exclu les victimes de traumatismes et celles qui étaient âgées de plus de 30 ans. Les patients ont été soumis à une évaluation normale, incluant des radiographies au besoin. Au moment du diagnostic final et ne connaissant pas le résultat du dosage du NT-proBNP, les médecins ont noté la probabilité que l'insuffisance cardiaque soit responsable de la dyspnée aiguë à l'aide d'une échelle de Likert en 7 points, dont les données furent par la suite réduites en trois catégories aux fins de l'analyse statistique. Le résultat principal était la concordance entre l'impression clinique et le dosage du NT-proBNP classifié selon les limites d'inclusion spécifiques à l'âge recommandées par le manufacturier. Les limites d'inclusion proposées plus récemment dans une autre étude furent aussi évaluées.

Résultats : Cent vingt-neuf patients ayant fait 139 visites à l'urgence furent inclus dans l'étude (âge médian de 76 ans; 59 % admis). Le dosage du taux sérique de NT-proBNP était positif dans 119 cas (86 %, intervalle de confiance [IC] à 95 %, 80 %–91 %), incluant 75 % des cas (43/57, IC à 95 %, 62 %–86 %) que le médecin traitant n'attribuait pas à l'insuffisance cardiaque, et 86 % des cas (25/29, IC à 95 %, 68 %–96 %) où le médecin traitant n'était pas certain du diagnostic. La concentration médiane de NT-proBNP était plus élevée chez les patients dont les résultats cliniques portaient à évoquer un diagnostic d'insuffisance cardiaque plutôt que de pneumonie ou de maladie pulmonaire obstructive chronique; cependant, les fourchettes de ces valeurs se chevauchaient grandement (médiane de 4 361 pg/mL; intervalle interquartile [IIQ] 2 386–10 877 par rapport à une médiane de1 651 pg/mL; IIQ 370–4 745, respectivement).

Conclusions : Il existe une discordance importante entre l'impression clinique des médecins traitants et les concentrations de NT-proBNP, notamment chez les patients que l'on ne croit pas atteints d'insuffisance cardiaque. Bien que la norme de référence du diagnostic à l'urgence soit imparfaite, le large chevauchement dans les concentrations de NT-proBNP suggère une mauvaise spécificité chez cette population cible à l'étude. L'implantation du dosage de routine du NT-proBNP à l'urgence en utilisant les limites d'inclusion actuelles devrait entraîner des coûts indirects importants découlant d'épreuves diagnostiques supplémentaires. Il n'est pas encore évident que l'implantation de cette méthode diagnostique aurait un impact positif sur les résultats pour les patients cliniquement pertinents.

Introduction

B-type natriuretic peptide (BNP) is a cardiac neurohormone released by the ventricles during systolic dysfunction or ventricular wall stress. Several recent studies have found a correlation between elevated BNP levels and the presence and severity of heart failure (HF) and left ventricular (LV) dysfunction.[1–4] Higher BNP levels are associated with increased mortality and morbidity for outpatients with HF, an effect that is independent of other cardiac markers, including troponin.[5,6] In clinical trials involving emergency department (ED) patients with dyspnea, BNP levels have been touted to be as good or better than physician judgment for the diagnosis of HF in acutely dyspneic patients.[7–10] However, concerns have been raised that the inclusion of patients with obvious HF in these trials resulted in an overestimation of the clinical utility of the test, particularly for patients in whom the diagnosis was unclear.[11,12]

BNP is synthesized as a pre-prohormone protein, proBNP. Upon release from cardiac myocytes, this protein is cleaved into BNP and its *N*-terminal fragment, NT-proBNP.[13] It has been suggested that NT-proBNP would have greater clinical utility than BNP because the former is larger, more rapidly detected and more biologically stable.[14] Recent studies have found a high correlation between serum NT-proBNP and BNP concentrations in both dyspneic ED patients[14] and clinic patients with established HF.[15]

Prior to adopting a new diagnostic test, it is essential to estimate the diagnostic performance and impact of the test on current practice, particularly in the target population of most interest. A test that could accurately identify HF when the clinician does not suspect it, or is unsure, would

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represent a major advance. Investigators have suggested that the natriuretic peptides BNP and NT-proBNP have the potential to play such a role in the diagnosis of HF.[16–18] The purpose of this study was to estimate the potential impact of NT-proBNP measurement on ED evaluation of patients presenting with acute dyspnea by quantifying the disagreement between physician impression and serum NT-proBNP levels.

Methods

Study design, population and setting

This prospective cohort study enrolled a convenience sample of patients with self-reported acute onset shortness of breath presenting to the ED of Kingston General Hospital, a tertiary care, university-affiliated institution with 55 000 annual ED visits. There were no prespecified criteria for symptom duration. Research nurses were instructed to consider enrolling any patient whose primary complaint was shortness of breath and in whom HF was a potential diagnosis. These enrolment criteria were designed to be inclusive and simple to replicate the real-world use of NT-proBNP testing.

Enrolment took place during research nurse availability (0800 to 2300, Monday through Friday) between January 2004 and May 2004. Subjects were identified by the research nurse upon their arrival at the ED; unstable or intubated patients were eligible for enrolment. Patients involved in trauma and those younger than 30 years of age were excluded. The study was approved by the institutional Research Ethics Board, and consent was not deemed necessary.

Study protocol

There was no intervention in standard care for eligible patients, with the exception of the addition of NT-proBNP testing. Patients underwent chest radiography, ECG and laboratory testing at the treating physician's discretion. Treating physicians and other ED staff were blinded to the NT-proBNP assay results. The test was added to routine bloodwork by the research nurse after identifying eligible patients. Prior to patient discharge or transfer to an inpatient ward, research nurses interviewed the attending emergency physician or senior emergency medicine resident caring for the patient. Physicians answered 2 questions using a 7-point Likert scale: Question #1 "Is this patient's dyspnea due to congestive heart failure?" and Question #2 "Could congestive heart failure be a contributing factor in this patient's ED visit?" For analysis purposes, the responses on this 7-point scale were subsequently collapsed into 3 categories: Likely HF (top 2 points), Unsure (middle 3 points) and Unlikely HF (bottom 2 points). Physicians also recorded their primary diagnosis and any secondary diagnoses. Prior to answering study questions, they were encouraged to review the results of standard diagnostic testing, as well as the response to therapy. Results of the NT-proBNP tests were not available to treating physicians during the patient's hospital stay, as these results were for study purposes only, and were not part of the patient medical record or computer-based laboratory records.

Two hundred assay kits were donated by Roche Diagnostics Canada for this study, and no sample size calculation was performed. Unused serum samples collected during the routine emergency evaluation of enrolled patients were immediately frozen and subsequently batch assayed within 1 month of the ED visit. A random subset of 29 samples was analyzed on at least 2 separate occasions to evaluate interassay variability and ensure biologic stability of the frozen samples.

Structured hospital record review was performed using explicit definitions at least 9 months after the initial ED visit by a single reviewer blinded to the study objectives. The following outcomes were recorded for the initial and any subsequent visits: death; hospital admission or ED revisit with subsequent diagnosis of HF; echocardiographic findings; and referral to an HF clinic.

Outcome measures

All outcomes were established a priori. The primary outcome was the agreement between the physician scoring of the likelihood of HF (Likely, Unsure and Unlikely) and the serum NT pro-BNP concentration (positive or negative by the manufacturer-recommended age-specific cut-off). After enrolment was completed, a major study (the PRIDE Study) was published in 2005 that proposed different age-specific cut-offs, including an indeterminate range.[16] Therefore, we also analyzed our data using these newly proposed cut-offs that result in 3 categories: positive, negative, and indeterminate. The secondary outcome was the frequency of relevant HF-related end points in patients determined to have a low or unsure likelihood of HF by the emergency physician or senior emergency resident, particularly patients with abnormal serum NT-proBNP concentrations.

Data analysis

Descriptive statistics were summarized using means and medians with 95% CIs and interquartile ranges (IQRs). Because of the anticipated positive skew in serum NT-proBNP concentrations, all values were log-transformed

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before analysis, but are reported on a normal scale for clarity. Statistical analysis was carried out with SPSS (v. 12.0).

Results

Data on 156 patient encounters were obtained during the study period, however 17 encounters did not include the performance of NT-proBNP testing and, thus, were excluded. Complete data were available for 139 visits by 129 patients (10 patients were enrolled twice on 2 separate visits), and this constituted the study population. Demographic data and the primary ED diagnoses for the study population are shown in Table 1. The median (IQR) interassay percentage of variation for the NT proBNP assay was 1.28% (0.70%, 2.21%).

Table 2 shows the agreement between the physician assessment that HF was the cause of the patient's dyspnea and the serum NT-proBNP qualitative test result for each of the 2 cut-off approaches studied. There was a high correlation between the results for Question #1 and Question #2, thus only the data from Question #1 (i.e., "Is this patient's dyspnea due to congestive heart failure?") are presented. Of note, using the manufacturer suggested cut-offs, 86% (95% CI, 80%–91%) of all patients had positive NT-proBNP results, including 75% (95% CI, 64%–87%) of patients who were considered unlikely to have HF. Using cut-offs established by the PRIDE Study,[16] 71% (95% CI, 63%–78%) of all patients had positive NT-proBNP results, including 49% (95% CI, 42%–56%) of patients who were considered unlikely to have HF. A further 14% of all patients and 21% of those who were considered unlikely to have HF had indeterminate NT-proBNP results based on the PRIDE Study cut-offs.

Figure 1 illustrates the distribution of serum NT-proBNP concentrations compared with the physician assessment of the likelihood of HF being the cause of the patient's acute dyspnea. Although NT-proBNP concentrations generally increased with increasing physician-assessed likelihood of HF, there is substantial overlap between categories. Figure 2 illustrates serum NT-proBNP concentration, categorized by primary ED diagnosis. Although NT-proBNP concentrations were higher in patients felt to have HF (median 4361 pg/mL; IQR 2386–10877) compared with those felt to have lung disease (1651 pg/mL; IQR 370–4745), these ranges for these groups also overlapped substantially.

Table 3 shows the outcomes of the 127 patients (98%) in whom complete follow-up data were obtained. Sixty-five (51%) of the 127 patients reviewed had experienced one of the a priori-specified HF-related events. Table 4a and Table 4b show these HF outcomes categorized by qualitative NT-proBNP test results using both the manufacturer suggested cut-off (Table 4a) and the PRIDE published cut-

Table 1. Characteristics of patients presenting to Kingston General Hospital emergency department (ED) with acute dyspnea who were enrolled in the prospective cohort study, January to May 2004

Variable	No. (and %) of patients*	Median NT-proBNP, pg/mL (and IQR)
Total no. of patient visits	139	
No. of repeat visits†	20	
Characteristic		
Median age, yr (IQR)	76 (66–83)	
Male	71 (51)	
Arrival via ambulance‡	63 (45)	
Positive pressure ventilation (intubated or BiPAP/CPAP)§	7 (5)	
Referred for admission	82 (59)	
Primary ED diagnosis		
Heart failure	55 (40)	4361 (2386–10877)
Lung disease	53 (38)	1651 (370–4745)
Shortness of breath, NYD	16 (12)	456 (106–1174)
Acute coronary syndromes	7 (5)	2497 (606–24474)
Other	5 (4)	185 (71–944)

IQR = interquartile range; BiPAP = bilevel (biphasic) positive airway pressure; CPAP = continuous positive airway pressure; NYD = not yet diagnosed
*Unless otherwise specified.
†10 patients had repeat visits.
‡Mode of arrival not documented on 7 (5%) of charts.
§Documentation of airway intervention incomplete in 6 (4%) of charts.

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Table 2. NT-proBNP test results using both manufacturer suggested cut-offs and PRIDE Study[16] cut-offs versus emergency department physician assessment of heart failure

Suggested cut-off	Physician assessment, no. (and %) of patients: Likely *n* = 53	Unsure *n* = 29	Unlikely *n* = 57	Total *N* = 139
Manufacturer				
Positive	51 (96)	25 (86)	43 (75)	119 (86)
Negative	2 (4)	4 (14)	14 (24)	20 (14)
PRIDE Study				
Positive	48 (91)	22 (76)	28 (49)	98 (71)
Unclear	4 (8)	3 (10)	12 (21)	19 (14)
Negative	1 (2)	4 (14)	17 (30)	22 (16)

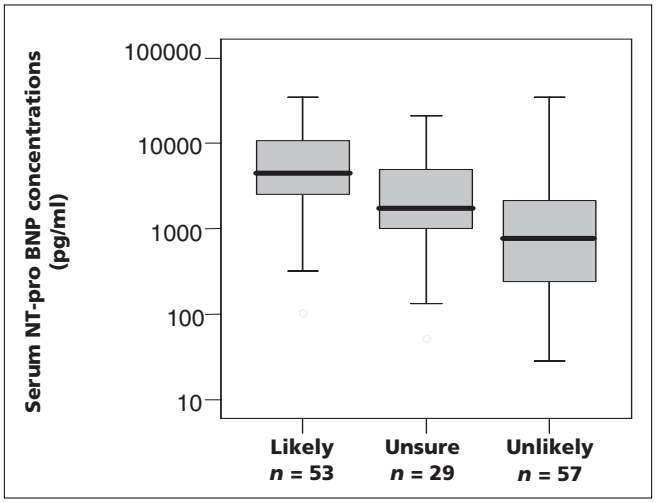

Fig. 1. Boxplots of serum NT-proBNP concentrations plotted against the physician assessment of the likelihood of heart failure causing the patient's symptoms. Footnote: Boxplots show the sample median using a solid line within the box, with the upper and lower edges (hinges) of the box representing the 75th and 25th percentiles (i.e., the interquartile range), and the extended lines (whiskers) representing the remainder of the data.

offs (Table 4b). Using the data in these tables, likelihood ratios can be calculated to quantify the utility of NT-proBNP in predicting HF-related events the patient population studied. For example, in the group of 26 patients diagnostically categorized as Uunsure by physicians, the NT-proBNP test using the manufacturer's cut-off has an LR(+) (positive likelihood ratio) of 1.27 (0.89–1.82) and an LR(–) (negative likelihood ratio) of 0.86 (0.14–5.2). Similar results were found using the PRIDE cut-offs, which yielded an LR(+) of 0.93 (0.65–1.33) and an LR(–) of 1.39 (0.28–7.05).

Discussion

Heart failure is a common ED presentation and is associated with considerable morbidity and mortality. It can be

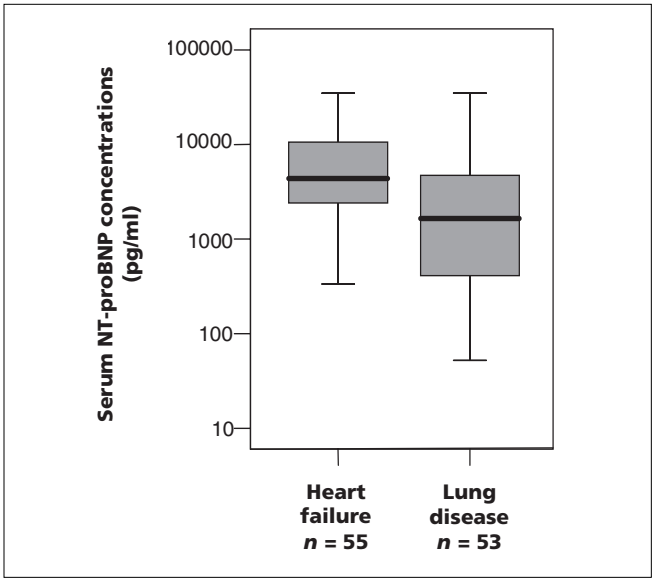

Fig. 2. Boxplots showing serum NT-proBNP concentrations for patients diagnosed with heart failure compared to those diagnosed with lung disease at the completion of ED assessment. Footnote: See Fig. 1.

Table 3. Data at ≥9 months for the 127 (of 129) patients enrolled in the study for whom complete follow-up data were available

Clinical likelihood of HF, no. of patients	No. of patients (%): Expired (all causes) *n* = 22 (17)	All admissions with HF mentioned *n* = 39 (31)	Referral to HF clinic for follow-up *n* = 20 (16)	Ejection fraction <50% 35/78 (45)	HF diagnosed on ED revisit *n* = 23 (18)	Combined outcome* *n* = 65 (51)
Likely, 48	9	28	14	21	15	40
Unsure, 26	6	6	4	8	4	14
Unlikely, 53	7	5	2	6	4	11

*Any of: hospital admission with HF; HF clinic visit; ejection fraction <50% on echocardiography; or ED revisit with HF.

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challenging to diagnose, particularly in patients with comorbidities such as chronic lung disease. Our findings support the observation of others[11] that, at the completion of standard ED evaluation, uncertainty persists regarding the possibility of HF in a substantial number of patients with acute dyspnea.

We observed that the great majority of acutely dyspneic patients in our ED had positive qualitative NT-proBNP results based both on the manufacturer guidelines (86% positive) or the more recent PRIDE Study cut-offs (71% positive). Moreoever, we found a significant degree of discordance between clinical judgment and NT-proBNP levels, particularly in patients who the physician believed did not have HF.

Is it possible that the NT-proBNP test correctly identified all patients with HF in our ED? Is it possible that between 70%–86% of acutely dyspneic patients in our centre had HF, and that a substantial proportion of them were misdiagnosed with conventional assessment? No previous study has suggested that HF accounts for more than two-thirds of acutely dyspneic ED patients.[14,16,18] Additionally, if HF truly was the diagnosis in more than two-thirds of our sample, other diagnoses such as chronic obstructive pulmonary disease and pneumonia would by extension be far less prevalent than generally found in such a population. It seems unlikely our study had an enrolment bias; the distribution of initial ED diagnosis and outcomes we found is very similar to other large single and multicentre validation trials of BNP and NT-proBNP tests.[16,19,20] Our 9- to 12-month follow-up identified outcomes consistent with a diagnosis of HF in approximately 50% of all patients, and most notably in 19% of patients in the Unlikely HF group. The NT-proBNP test was abnormal in many (but not all) of these patients, along with a substantial number of other patients without significant outcomes. Based on our findings, we speculate that routine testing for NT-proBNP in acutely dyspneic patients using current cut-offs is likely to result in substantial indirect costs from further testing in Unsure and Unlikely HF patients, with unclear if any benefit for those few missed HF patients.

The recently published PRIDE Study[16] examined the utility of NT pro-BNP in addition to clinical judgment (assessed using a 0%–100% estimate of pre-test probability) in a similar group of dyspneic ED patients. Using receiver operating characteristic (ROC) curves, the authors of this study concluded that the addition of NT-proBNP to standard assessment would improve diagnostic accuracy compared with using clinical judgment alone (an area under the curve [AUC] of 0.90 for clinical judgment v. 0.94 for NT-proBNP and 0.96 for both combined). Although the use of a continuous scale to assess the treating physician's determination of the pre-test probability of HF allows ROC generation, it does not accurately replicate the clinical decision-making faced by clinicians. Practically speaking, clinicians must classify patients as those with HF, those without HF and those in whom the diagnosis is unclear. This interpretation of the nature of clinical decision-making and patient categorization is supported by both the Breathing Not Properly (BNP) Multinational Study[9] and a recent commentary.[11] Indeed, in patients in whom the pre-test probability of HF

Table 4a. Heart failure–related outcomes of the 127 patients, ranked according to the clinical likelihood of heart failure (HF) compared with their NT-proBNP result, as defined by the manufacturer's suggested age-specific cut-off

Clinical likelihood of HF, no. of patients	HF-related outcome, NT-proBNP test result			
	Outcome present *n* = 65		Outcome absent *n* = 62	
	Positive	Negative	Positive	Negative
Likely, 48	39	1	7	1
Unsure, 26	12	2	10	2
Unlikely, 53	11	0	28	14

Table 4b. Heart failure–related outcomes of the 127 patients, ranked according to the clinical likelihood of heart failure (HF) compared with their NT-proBNP result, as defined by the PRIDE Study[16] age-specific cut-offs*

Clinical likelihood of HF, no. of patients	HF-related outcome, NT-proBNP test result					
	Outcome present *n* = 65			Outcome absent *n* = 62		
	Positive	?	Negative	Positive	?	Negative
Likely, 48	38	2	0	5	2	1
Unsure, 26	10	1	3	10	1	1
Unlikely, 53	8	1	2	16	11	15

*PRIDE Study age-specific cut-offs include an indeterminate range.

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was estimated to be very high by ED physicians (>95%) the actual prevalence of HF was 95%. Conversely, when the pre-test probability was estimated to be <5%, or very low, the prevalence of HF was 7%. In the wide range of pre-test probability between these extremes (i.e., 5%–94%) the prevalence of HF ranged from 21%–52%,[11] which underscores the problems with a percentage pre-test probability approach. A recent systematic review in the *Journal of the American Medical Association* generated LRs for the clinical judgment of physicians in assessing the likelihood of HF in dyspneic ED patients.[21] When the physician diagnosed the patient with HF, the LR(+) was 4.4 (95% CI, 1.8–10.0). Conversely, when the patient was deemed to be unlikely to have HF, the LR of HF was 0.45 (95% CI, 0.28–0.73). Thus clinician judgment for these Unsure HF patients offers moderate diagnostic information.

Although the PRIDE Study represents an important contribution to the literature on this topic,[16] independent validation of cut-offs arising from a study of this nature is a critical step that must occur before the widespread implementation of a diagnostic test.[22] The PRIDE investigators derived optimal cut-offs for their patient population using an age-stratified analysis and selected the levels that yielded the best sensitivity and specificity in their patient population. Applying the PRIDE cut-offs to our data improved the test performance relative to the manufacturer suggested cut-offs, but still resulted in a high level of discordance between NT pro-BNP and physician impression. Moreover, much of this improvement came at the expense of introducing an indeterminate zone to the test result.

An additional concern with widespread implementation of cardiac biomarkers such as BNP and NT-proBNP is the potential for misdiagnosis. Significantly abnormal BNP results (well above 100 pg/mL), deemed to be false-positives, have been found in patients with sepsis and pulmonary embolism.[23,24] Clinical outcomes of patients with either sepsis or pulmonary embolism who are presumed to have HF and are treated accordingly could be catastrophic.

It has been suggested that the very low LRs of HF with very low BNP and NT-proBNP values make a negative BNP or NT-proBNP result a very useful rule-out test in the low or unclear pre-test probability patient.[11] Although we do not necessarily disagree with this suggestion, a rule-out test with such poor specificity will increase costs through further work-up and investigation for many low pretest probability patients. Although it has been suggested that the implementation of BNP as an ED test reduces costs and hospital admissions,[17] information on important clinical outcomes is still lacking. Future research must examine the impact of BNP or NT-proBNP testing on clinical outcomes for ED patients before any adoption of this test into routine ED care.

Limitations

The limitations of our study include the fact that the study population was recruited at a single centre and, accordingly, the clinical assessments, case mix and outcomes may not be generalizable to other centres. Additionally, we did not obtain an independent adjudicated assessment of the most accurate diagnosis for our patients (a gold standard comparison). Although this study was not designed to validate the diagnostic accuracy of NT-proBNP, but rather was designed to estimate the impact of adding it to our laboratory panel, we attempted to address this limitation by conducting a 9-month follow-up using a structured chart review for relevant clinical outcomes. Finally, we elicited the physician assessment of the likelihood of HF using a 7-point Likert scale, which we collapsed into 3 categories for the purposes of analysis. It is possible, though unlikely, that some precision in the estimates of the diagnostic accuracy of the physician judgment was lost through this simplification.

Conclusion

Serum NT-proBNP levels are positive in the large majority of acutely dyspneic patients, including patients in whom physicians feel that HF is unlikely. The addition of this test to routine ED assessment of such patients can be anticipated to lead to substantial increases in outpatient or inpatient testing and follow-up. It remains unclear whether the introduction of this diagnostic test would have a positive impact on clinically relevant patient outcomes.

Competing interests: None declared.

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