BMJ Open A prospective cohort study to refine and validate the *Panic Screening Score* for identifying panic attacks associated with unexplained chest pain in the emergency department

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ABSTRACT

Introduction: Panic-like anxiety (panic attacks with or without panic disorder), a highly treatable condition, is the most prevalent condition associated with unexplained chest pain in the emergency department. Panic-like anxiety may be responsible for a significant portion of the negative consequences of unexplained chest pain, such as functional limitations and chronicity. However, more than 92% of panic-like anxiety cases remain undiagnosed at the time of discharge from the emergency department. The 4-item *Panic Screening Score* (PSS) questionnaire was derived in order to increase the identification of panic-like anxiety in emergency department patients with unexplained chest pain.

Methods and analysis: The goals of this prospective cohort study were to (1) refine the PSS; (2) validate the revised version of the PSS; (3) measure the reliability of the revised version of the PSS and (4) assess the acceptability of the instrument among emergency physicians. Eligible and consenting patients will be administered the PSS in a large emergency department. Patients will be contacted by phone for administration of the criterion standard for panic attacks as well as by a standardised interview to collect information for other predictors of panic attacks. Multivariate analysis will be used to refine the PSS. The new version will be prospectively validated in an independent sample and inter-rater agreement will be assessed in 10% of cases. The screening instrument acceptability will be assessed with the *Ottawa Acceptability of Decision Rules Instrument*.

Ethics and dissemination: This study protocol has been reviewed and approved by the Alphonse-Desjardins research ethics committee. The results of the study will be presented in scientific conferences and published in peer-reviewed scientific journals. Further dissemination via workshops and a dedicated website is planned.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study protocol is based on well-established methodological standards.
- While great efforts were made to ensure inclusion of the most relevant predictors of panic-like anxiety, it is possible that some unidentified but relevant variables were missed.

INTRODUCTION

Chest pain in Emergency Medicine

Chest pain accounts for approximately 5% of all emergency department (ED) consultations,¹ and over 50% of cases remain unexplained at discharge.^{2–6} In Canada, approximately 400 000 patients/year present in the ED with unexplained chest pain (UCP).^{2 4}

Burden of UCP

Despite a generally favourable prognosis, 80% of cases of UCP persist for up to 12 years after initial medical evaluation.^{7–13} Many patients with UCP (41–60%) report limitations in daily functioning (eg, housework, walking and exercising) and work absenteeism or disability (17–35%).^{7 8 10–12 14–22} Moreover, the occupational impairments associated with UCP are comparable or more severe than those associated with cardiac chest pain.^{7 22} The negative impact of UCP on quality of life and day-to-day functioning is considerable and may be observed for up to 10 years after symptom onset.^{7–9 11 12 14–22}

Despite the benign origin of their pain, patients with UCP report persistent fear of serious health conditions.^{11 20 22 23} They are frequent users of healthcare services, including emergency care, and often

undergo multiple invasive tests (eg, coronary angiograms).^{9 14 22 24–27} In Canada, the average duration of an ED consultation for a UCP patient is 11 h and one in four patients arrives in the ED by ambulance.³ The direct annual cost associated with UCP in the USA is estimated to amount to eight billion US dollars.^{28 29}

UCP is also associated with significant psychological distress that can become chronic in the absence of targeted interventions.^{30–32} In fact, 20–40% of patients present a psychiatric disorder at the time of ED consultation^{3 6 33–35} and 15% report suicidal ideation.^{3 33 34 36} Unfortunately, fewer than 5% of patients are referred to a mental health professional for psychiatric or psychological treatment.³

While the cause of UCP may be unclear, the literature clearly demonstrates that UCP is highly prevalent and often chronic, and that it constitutes a significant burden for patients and society alike.

Aetiology of UCP

Although pathologies such as microvascular angina and gastroesophageal reflux may be at the origin of some cases of UCP,²⁹ panic attacks are the most prevalent condition associated with UCP in ED.^{3 34 35 37–39} As many as 44% of patients with UCP experience panic attacks in the month prior to ED consultation.^{3 34 35 37–39}

A panic attack is defined as a discrete period of intense fear or discomfort that peaks in a few minutes.^{40 41} Fear or discomfort is accompanied by at least four of the following symptoms: chest pain, palpitations, dyspnoea, a feeling of suffocation, hot or cold flashes, sweating, nausea, feeling faint, paraesthesia, trembling, fear of death, depersonalisation and fear of losing control or going crazy.^{40 41} Panic attacks may be an isolated phenomenon or may occur in the context of a psychiatric disorder; the most common psychiatric disorder in which panic attacks occur is panic disorder.⁴² The 1-year prevalence of panic attacks in the general adult population is 8–11%;^{42 43} the prevalence is four to six times higher among patients presenting with UCP.^{3 42 43}

The literature clearly demonstrates that panic attacks with and without panic disorder constitute a significant mental health problem with serious consequences.^{3 36 42–47} For simplicity, the term *panic-like anxiety* (PLA) will be used to refer to panic attacks with or without panic disorder.

Consequences of PLA in patients with UCP

PLA may be responsible for a significant portion of the negative consequences of UCP.^{3 6 15 30–32 34 35 37} PLA is associated with a greater frequency of UCP episodes and increased risk of chronicity.^{15 30–32} Quality of life is lower and functional limitations levels are higher in patients with UCP and PLA.^{15 30 31 37} Moreover, in patients with UCP, PLA is associated with at least a threefold increase in psychiatric morbidity and suicidal ideation.^{3 34} Similarly, use of medical resources nearly doubles when PLA is present.^{31 32}

In patients with UCP, PLA is associated with elevated morbidity, excessive health services use and a negative prognosis. Unfortunately, more than 92% of cases of PLA remain undiagnosed at the time of discharge from ED.^{3 34 35}

Identifying PLA in patients with UCP

Several factors may contribute to the current low rate of PLA identification in patients in ED. First, PLA patients and physicians alike tend to focus on physical symptoms and on potential organic causes.⁴⁸ Second, the identification of PLA is complicated by the similarity between PLA symptoms and symptoms of medical conditions such as coronary artery disease. Third, the limited time available for clinical evaluation in ED settings may be insufficient to identify psychological causes of symptoms.⁴⁹ Finally, some ED physicians are unfamiliar with PLA or believe that it is not their role to identify psychiatric problems.⁵⁰ However, other physicians recognise the importance of improving identification and treatment of PLA in the ED settings.^{51–53}

Researchers and clinicians seeking methods for increasing PLA identification rates must take into consideration certain constraints related to the clinical practice of emergency medicine, notably the brief period of time available to assess patients.

Importance of screening for PLA in ED patients with UCP

Increasing the rate of identification of a problem is not in itself sufficient to improve clinical outcomes for patients.^{54 55} Gates⁵⁴ and Stiell and Wells⁵⁵ propose five criteria for determining the importance of a detection procedure and its potential impact on patients' clinical outcomes: (1) the problem has an impact on public health; (2) the problem is sufficiently prevalent; (3) effective treatments are available to reduce morbidity; (4) early diagnosis improves patient prognosis and (5) additional investigations or treatments are acceptable to patients.

The current data demonstrate that more accurate identification of PLA in ED patients with UCP could improve clinical outcomes. First, PLA in patients with UCP is a prevalent health problem with serious consequences for patients and society. Second, research demonstrates that morbidity associated with PLA in patients suffering from UCP can be greatly reduced via evidence-based treatments.^{56–58} For example, 80–95% of patients with PLA show significant improvement and attain an adequate level of functioning following cognitive-behavioural therapy.^{57 59 60} Several evidence-based treatment methods for PLA have proven to be effective in patients with UCP.^{38 61–63} Third, given that PLA tends to worsen over time,^{32 42 64–67} negatively influencing treatment response, early diagnosis improves prognosis.^{25 42 64 66 68–71} Finally, the criterion of acceptability to patients appears to have been met. Participation rates for patients with PLA and UCP approached for inclusion in a study are generally over

70%.^{38 61–63} In addition, 80% of primary care patients with PLA agreed to receive psychiatric care.⁷²

The development of interventions designed to improve identification of PLA associated with UCP in ED appears to be indicated. A central factor for such an intervention is the availability of a suitable screening instrument, that is, an instrument that is efficient and acceptable to emergency physicians.^{54 55} The use of decision aids such as screening instruments is recognised as an effective method for improving clinical decision-making.⁵⁵

Panic Screening Score

To our knowledge, our team has developed the only two screening instruments for PLA in ED patients with UCP.^{73 74} One instrument, the *Panic Screening Score* (PSS; figure 1), was designed for use with patients with UCP and identifies panic attacks with and without panic disorder.⁷³ In addition, the PSS has the advantage of being brief (four items) and easy to use. We have shown that the PSS is eight times more sensitive in detecting PLA associated with UCP than is clinical evaluation by an emergency physician.^{3 73} In addition, the PSS offers a good combination of sensitivity and specificity (table 1) and these properties have been shown to be stable in a retrospective validation and preliminary prospective validation.^{73 75} As of now, the PSS is the briefest and most effective screening instrument for PLA associated with UCP in emergency settings. Although the PSS has good specificity, its sensitivity needs to be improved (table 1).

Summary

Early identification of PLA in ED patients with UCP appears to be the strategy of choice for reducing morbidity, chronicity and overuse of healthcare services. The PSS is a concise and effective instrument that represents the most promising method for achieving this objective.

- 1) Does the patient have a history of anxiety disorders?
Yes = 7
No = 0, ask other questions.

2) Please indicate how often this thought occurs when you are nervous:
"I will choke to death."
0: Never occurs, 2: Rarely occurs, 4: Occurs during half the times,
6: Usually occurs, 8: Always occurs.

3) Did the patient arrive in the ED by ambulance?
Yes = 3
No = 0

4) Please answer the statement by circling the number that best applies to you.
"When I notice my heart beating rapidly, I worry that I might be having a heart attack."
0: Very little, 1: A little, 2: Some, 3: Much, 4: Very much.

Scoring:
➤ Total score = sum of all items value
➤ A total score ≥ 6 indicates probable panic.

Figure 1 The Panic Screening Score (PSS) questionnaire.

The present study will represent a major step towards the clinical application of the PSS and the early diagnosis and treatment of PLA in ED patients with UCP.

METHODS AND ANALYSIS

Objectives

The objectives of this prospective cohort study are to (1) refine the PSS; (2) validate the revised version of PSS in an independent sample; (3) estimate the reliability of the revised PSS and (4) assess the acceptability of the instrument among ED physicians.

Methodological framework

The research methods and statistical analyses used in this study are based on clinical decision rule standards⁵⁵:

1. The outcome must be clearly defined and assessed blindly;
2. The predictors must be clearly defined, standardised and evaluated without knowledge of patient status;
3. The reliability of the variables studied must be demonstrated;
4. Participants must be selected without bias and must represent a large range of clinical and demographic characteristics. Ideally, the study should be conducted in several centres in order to increase external validity;
5. Appropriate statistical analyses must be used;
6. The sample size must be sufficient to permit valid statistical analyses;
7. The sensibility of the instrument must be adequate. It must have a clear objective, good content validity and clinical relevance, and must be easy to use in the context of targeted practice;
8. The capacity of the instrument to identify patients with (sensitivity) and without (specificity) the condition must be demonstrated;
9. Measures must be taken to guarantee the appropriate application of the instrument.

The procedures for refining the PSS (objective 1) are based on Stiell and Wells⁵⁵ recommendations. First, the PLA predictors that were valuable but not essential in previous studies will be reassessed.⁷³ Next, the potential predictors of PLA that were not assessed at the time of the initial study will be evaluated.

Participants

This study will consecutively recruit 3000 patients at the two emergency services of the Centre de santé et de services sociaux Alphonse-Desjardins (University-Affiliated Hospital of Lévis and Paul-Gilbert Hospital). To be eligible, patients will have to present UCP as defined by (1) the absence of an identifiable cause (eg, pneumothorax, pneumonia); (2) absence of chest trauma; (3) absence of new malignant cardiac arrhythmia and (4) a score of 2 or less on the modified version of the *thrombolysis in myocardial infarction score*.^{76 77} This simple instrument stratifies patients presenting chest pain according to the

Table 1 Predictive validity of the PSS⁷³

	Derivation (n=201)	Retrospective validation (n=305)
Sensitivity	63% (95% CI 52 to 73%)	53% (95% CI 44 to 62%)
Specificity	84% (95% CI 76 to 90%)	85% (95% CI 78 to 89%)
Positive predictive value	74% (95% CI 62 to 83%)	72% (95% CI 62 to 80%)
Negative predictive value	76% (95% CI 68 to 89%)	71% (95% CI 65 to 77%)
Positive likelihood ratio	3.89 (95% CI 2.5 to 6.05)	3.45 (95% CI 2.35 to 5.04)
Negative likelihood ratio	0.44 (95% CI 0.33 to 0.59)	0.55 (95% CI 0.46 to 0.67)

PSS, Panic Screening Score.

probability of mortality or myocardial infarction in the 30 days following the ED visit.^{76–78} A result ≤ 2 is associated with low incidence (3%) of mortality or cardiac events; scores >2 are associated with a higher incidence (28%). Scores are obtained by summing values that correspond to the following characteristics: (1) age ≥ 65 years (1 point); (2) known coronary stenosis $\geq 50\%$ or history of revascularisation (1 point); (3) deviation of the ST segment ≥ 0.5 mm (5 points) and (4) elevated rate of cardiac enzymes defined as troponins I ≥ 99 th centile.⁷⁷ A value of zero is assigned for criteria 3 and 4 if the physician does not order the tests necessary to obtain the information.

Patients will be excluded if they (1) present a terminal illness; (2) present a severe communication problem that could interfere with the administration of the questionnaire; (3) present a psychotic state, major cognitive deficit or other condition that could invalidate the interview and (4) are legally incompetent or younger than 18 years of age.

Procedure

With the assistance of a research nurse, the emergency physicians will assess the eligibility of all patients presenting with UCP. Physicians will complete the PSS for every eligible and consenting patient. To assess the reliability of the PSS items, a second physician will independently complete the PSS for at least 10% of patients. As in other similar studies and due to constraints such as the availability of a second physician, the reliability assessment will be conducted using a convenience sample.^{79–81}

To assess the primary outcome and potential predictors of PLA, all participants will complete a telephone interview within 72 h following recruitment. Interviewers will be blind to the patient's PSS scores. Since the evaluation of the criterion standard will occur after the patient's discharge, physicians will be blind to the results of the PLA evaluations.

The research nurse will review the ED computerised database every day to ensure that all potentially eligible patients were assessed. A registered nurse will contact patients who were missed and request consent for the telephone interview. For non-consenting patients, only age, gender and time of ED visit will be recorded. This

step will enable us to identify potential selection biases and ensure quality control.

The acceptability of the PSS to emergency physicians will be assessed at the end of the study. The time taken to administer the PSS will also be evaluated in 10% of cases randomly selected. The initiation of the questionnaire will be defined as the moment the physician asks the first question; the end of the questionnaire will be defined as the moment the patient finishes answering the final question. This measure will be used to assess whether or not the PSS is sufficiently brief for the ED.

Measures

- *Eligibility evaluation form:* This form contains the inclusion and exclusion criteria. It also records the patient's contact information, age, gender and time of ED visit.
- *PSS and PSS—revised version:* The PSS score is calculated by summing the points assigned to the answer for each of the four questions. A score ≥ 6 is considered to be a positive result: the patient presents an elevated probability of PLA. A revised version of the PSS will be administered to patients during the validation phase (objective 2). The revised version will include only the items selected during the optimisation phase.
- *Anxiety disorders interview schedule for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (ADIS-IV):*^{82–83} The Panic disorder module of the French (or English) version of the interview will be administered by telephone. As recommended by experts in the field, ADIS-IV will serve as the criterion standard for the identification of PLA.⁸⁴ The Panic disorder module has shown excellent reliability for the identification of PLA ($k \geq 0.80$).³⁴ PLA is defined as either the presence of a panic attack during the previous month or the presence of panic disorder.⁷³
- *Additional predictors for the refinement phase (objective 1):* Additional predictors include the four potential predictors of PLA identified but not included in the final version of the PSS,⁷³ as well as the items selected following a pilot study⁷⁵ and a review of the literature:
 - Fear of dying associated with chest pain;^{85–86}
 - Item number 4 (fear of fainting) of the Anxiety Sensitivity Index^{87–88};

- Item number 28 (feeling overwhelmed by one's problems) on the State-Trait Anxiety Inventory;^{89 90}
 - The *Autonomic Nervous System Questionnaire*⁹¹;
 - The four panic disorder items from the Patient Health Questionnaire-15;⁹² these items were selected because they demonstrated sensitivity and specificity between 75% and 96% for PLA in patients in primary care and psychosomatic settings⁹³;
 - The modified version of the *Life Events Stress Scale*.^{94 95} This scale has an excellent internal consistency (0.87). The questionnaire includes 10 items, each of which corresponds to a category of stressful events. Patients are asked to specify whether or not each event has occurred and, if so, whether or not it occurred within the previous six months. For the purpose of this study, patients will be asked to specify whether or not the event occurred in the last month. The intensity of the stress associated with each event will be evaluated on a five-point Likert scale. This questionnaire was selected because the occurrence or aggravation of PLA is preceded by stressful life events in 80% of cases.⁹⁶
- ▶ Modified version of the *Ottawa Acceptability of Decision Rules Instrument* (OADRI)⁹⁷: This 12-item questionnaire assesses the acceptability of clinical decision rules by physicians. The questionnaire has good internal consistency (0.80–0.86) and good construct validity.⁹⁷ Ten items will be used in the present study as some information will not be available to ED physicians at the time of assessment. The first excluded item concerns the instrument's validation data; the second excluded item concerns the impact of the instrument on the use of clinical resources.
 - ▶ The PSS administration time assessment record sheet: This document includes instructions for assessing the PSS administration time and recording the result.

Quality control

Emergency physicians will receive a 30 min training session on how to use the PSS. The session will include an overview of the study, inclusion and exclusion criteria and guidelines for the administration of the PSS and for scoring patients' answers. The training session will be developed jointly with the Centre de liaison sur l'intervention et la prévention psychosociale. This non-profit organisation is specialised in knowledge transfer and dissemination of research results.

Over a 1-month period, a research nurse will periodically observe each physician as he or she administers the PSS, in order to obtain feedback and to identify problems. This step will be repeated during the implementation of the refined version of the PSS.

Telephone interviews will be conducted by graduate students in psychology. Each student will receive 1 day of training on the administration of ADIS-IV, followed by weekly supervision with a clinical psychologist. Telephone interviews will be recorded to facilitate

supervision. A random sample of 25% of recorded interviews will be used to evaluate inter-rater agreement on the diagnosis of PLA. During the optimisation phase (objective 1), the recordings will also be used to evaluate inter-rater agreement on each of the additional interview items. These supervision and inter-rater agreement procedures have been proven effective in our previous studies and generated excellent diagnostic reliability for PLA.^{3 34}

Data analysis

Participants' sociodemographic data will be presented in descriptive form. To evaluate the representativeness of the sample, participant data will be compared with data of the eligible patients who declined to participate. Continuous variables that meet the assumptions of normality will be analysed with Student's t test. Otherwise, Wilcoxon Mann-Whitney's non-parametric test will be used. The χ^2 test will be used for categorical variables. Inter-rater agreement for PLA diagnosis on ADIS-IV^{82 83} will be assessed with Cohen's κ coefficient.

As the predictive performance of a clinical rule is usually overestimated in the sample used in its development, it is important to evaluate the rule in an independent sample.^{55 98} In this study, a temporal validation procedure will be used. The refinement analyses (objective 1) will be conducted using data from the first 1500 patients; the validation of the refined version of the PSS (objective 2) will be performed using data from the subsequent 1500 patients.

Refinement of the PSS (objective 1)

The reliability of the four PSS items and the 15 potential predictors will be evaluated using Cohen's κ tests or weighted κ . Only the items with a good κ coefficient ($\kappa \geq 0.6$) will be included in further analysis.⁵⁵ We will use the two types of analysis recommended by experts in the field, recursive partitioning and regression,⁵⁵ to refine the PSS with data collected from the first 1500 patients. Recursive partitioning generally results in a more sensitive instrument, whereas regression yields models with a higher global predictive value.^{55 99}

This study will use the recursive partitioning technique known as Classification and Regression Trees.¹⁰⁰ The construction of Classification and Regression Trees will be automated, but manual intervention will be used if some of the concurrent predictors are more useful than others (eg, more reliable, more representative or easier to use). We will dichotomise continuous variables by selecting the most effective cut-off point for identifying patients with PLA.

Log-binomial regression analysis will also be performed. This type of analysis is preferred to logistic regression because it provides exact relative risks rather than ORs. Furthermore, when the prevalence of the dependent variable is greater than 10%, the estimate of the relative risk by logistic regression is imprecise.¹⁰¹ In this study, the expected prevalence of PLA is 44%.³

Variables associated with PLA in univariate log-binomial regression ($p \leq 0.15$) will be considered in the multivariate analysis. The multivariate log-binomial regression will be performed using the ascending stepwise method. Multicollinearity between variables will be verified. If correlations ≥ 0.80 are obtained, the analysis will be repeated using only one of the intercorrelated items, in order to obtain the most effective model. The regression equation will be converted into a score by assigning points to each answer; point assignment will be based on the magnitude of corresponding regression coefficients according to the *Framingham study risk score function*.¹⁰² The result is a simple score that provides probability estimates that correspond to the score generated by the multivariate regression model. The cut-off score that yields the best predictive validity will be selected based on the area underneath the receiver-operating characteristic (ROC) curve and the measures of predictive validity.

The calibration (Hosmer-Lemeshow test) and discriminating validity (area under the ROC curve, sensitivity, specificity, likelihood ratios, predictive values) of the two optimised versions of the PSS will be evaluated. CIs of 95% will be calculated for each of the discrimination measures. The version of the PSS that is simplest (ie, the version with the fewest items) and offers the best discrimination will be evaluated (objective 2).

Validation of the refined PSS (objective 2)

The refined version of the PSS will be prospectively validated in a validation sample ($n=1500$). Sensitivity, specificity, predictive values and likelihood ratios will be calculated with 95% CIs.

Evaluation of the PSS reliability

Cohen's κ coefficient will be used to assess the level of inter-rater agreement (reliability) for the refined PSS (presence or absence of PLA) and for each of its components. In the case of variables including three or more categories, a weighted κ coefficient will be calculated.^{73 103}

Acceptability of the PSS

Descriptive data on the PSS administration time will be reported, including the mean, median and range. The total score on the OADRI and the level of endorsement for each item will also be reported in descriptive form.

Justification of the sample size and feasibility

On the basis of our previous study, we estimate the minimum prevalence of PLA in these settings to be 40%.³ The sample composed of the first 1500 patients will be used for analyses related to the refinement of the PSS. It will include approximately 600 patients with PLA. This number exceeds the minimum ratio of 10 cases for each variable in the regression analysis.¹⁰⁴ A subsample of 1500 patients will allow us to obtain a CI of 95%

$\pm 3.9\%$, for a sensitivity equivalent to that reported in the original PSS study (63%).

The EDs at the Centre de santé et de services sociaux Alphonse-Desjardins receive approximately 110 000 patients each year, and approximately 2% of patients visiting the two EDs present UCP. Of 2200 eligible patients per year, we expect that 10% will be missed and 20% will decline to participate. Our final recruitment estimate is therefore 3000 participants in 24 months (1500/year).

ETHICS AND DISSEMINATION

The research ethics committee at the Centre de santé et de services sociaux Alphonse-Desjardins approved this protocol. The study will not affect usual care and the ethical considerations are minimal. Patients' verbal consent to complete the PSS and to be contacted by telephone will be solicited. Verbal consent will be obtained again at the time of the telephone interview. All data will be treated according to standard guidelines for ensuring patient confidentiality.

The results of the study will be presented in scientific conferences and published in peer-reviewed scientific journals. Further dissemination through workshops aimed at emergency physicians in clinical settings and a dedicated website is planned.

DISCUSSION AND CONCLUSIONS

This study is designed to validate an effective and efficient screening instrument for PLA in ED patients with UCP. The PSS will help emergency physicians determine the likelihood of PLA, in turn facilitating appropriate referrals to mental health professionals or family physicians for confirmation of the diagnosis and treatment. Treatment for PLA significantly reduces associated morbidity and excessive use of healthcare services, and has an overall favourable cost/benefit ratio.^{26 38 61–63 105–107} This study will result in a screening tool with the potential to have a tangible clinical impact for ED patients with UCP and PLA. Further research will focus on assessing the impact of use of the PSS and on validating the instrument in other settings, such as cardiology and primary care clinics.^{25 31}

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