New clinical prediction model for early recognition of sepsis in adult primary care patients: a prospective diagnostic cohort study of development and external validation

INTRODUCTION

Early recognition of sepsis is the critical factor influencing patient outcome.1–4 Protocols for the early identification of sepsis to trigger the administration of intravenous antibiotics successfully decreased sepsis-related mortality in emergency departments [EDs].3,6 In patients with community-acquired sepsis, GPs are often the first responding healthcare providers assessing patients.3,8 GPs’ recognition of sepsis and decision to refer a patient to the hospital is essential for adequate treatment. At the same time GPs have an essential role in preventing unnecessary referrals as hospital admission in itself can have a negative impact, especially in patients who are older or frail.

METHOD

Adult patients who were acutely ill and received home visits were included. A total of nine clinical variables were selected as candidate predictors, next to the biomarkers C-reactive protein, procalcitonin, and lactate. The primary endpoint was sepsis within 72 hours of inclusion, as established by an expert panel. Multivariable logistic regression with backwards selection was used to design an optimal model with continuous clinical variables. The added value of the biomarkers was evaluated. Subsequently, a simple model using single cut-off points of continuous variables was developed and externally validated in two emergency department populations.

RESULTS

A total of 357 patients were included with a median age of 80 years (interquartile range 71–86), of which 151 (42%) were diagnosed with sepsis. A model based on a simple count of one point for each of six variables (aged ≥65 years; temperature >38°C; systolic blood pressure ≤10 mmHg; heart rate >110/min; saturation ≤95%; and altered mental status) had good discrimination and calibration (C-statistic of 0.80 [95% confidence interval = 0.75 to 0.84]; Brier score 0.175). Biomarkers did not improve good discrimination and calibration (C-statistic of 0.80–0.81 for model with biomarkers).

CONCLUSION

Based on this study’s GP out-of-hours population, a simple model can accurately predict sepsis in acutely ill adult patients using readily available clinical parameters.

Keywords

after-hours care; clinical decision rule; diagnosis; general practice; sepsis; vital signs.
Currently GPs’ decisions to refer patients with severe infections to the hospital are based on an intuitive interpretation of signs, symptoms, and general impression of a patient.9,10 For primary care, up until now, there has been no diagnostic model available to support decisions to diagnose and manage sepsis. Clinical scores used in hospitals, like the quick Sequential Organ Failure Assessment (qSOFA),11 systemic inflammatory response syndrome (SIRS),12 or National Early Warning Score (NEWS)13 are not validated in primary care.

This study aimed to develop and validate a first diagnostic clinical model for the early recognition of sepsis in adults presenting in primary care. Ideally, patients with sepsis are identified early in the course of the disease and therefore the model will be designed to predict sepsis to be present within 72 hours. Immediate hospital referral is expected to improve outcome in these patients. This study investigated clinical signs, symptoms, and biomarkers potentially available at the bedside.

**METHOD**

**Setting**

Patients were enrolled between June 2018 and March 2020 at four participating out-of-hours primary care services in the central and south of the Netherlands (Ede, Den Bosch, Uden, and Oss). The combined area covers roughly 800,000 inhabitants in a mixed urban, suburban, and rural area. In the Netherlands, out-of-hours primary care is organised in large-scale primary care services serving between 50,000 and 400,000 inhabitants.14 Telephone triage is used to decide who needs to come to the clinic and who is visited at home. Only patients who received home visits were included in the study as these patients are usually more severely ill than other primary care populations. All participants (or legally authorised representatives of incapacitated patients) gave written informed consent for the study. The protocol for this study has been previously published15 and can be consulted for further details.

**Patients**

Acutely ill adult (aged ≥18 years) patients with fever, confusion, general deterioration, or otherwise suspected severe infection were eligible for inclusion. Patients were excluded if any of the following criteria were present:

- non-infectious diagnosis suspected as the cause of the acute complaints, for example, myocardial infarction or stroke;
- hospitalisation within 7 days before the home visit;
- a condition present requiring secondary care assessment regardless of the severity of infection, for example, neutropenic fever; and
- terminal illness or other reason not to be referred to the hospital, despite the presence of a life-threatening condition.

**Candidate predictors**

Based on other prediction models, sepsis guidelines, and triage protocols,11–13,16,17 nine clinical parameters were selected as candidate predictors. These included:

- age;
- tympanic temperature;
- systolic blood pressure;
- peripheral oxygen saturation;
- heart rate;
- respiratory rate;
- mental status (normal or altered);
- rapid progression of illness (yes/no); and
- rigors (yes/no).

Furthermore, three biomarkers were selected: lactate; C-reactive protein (CRP); and procalcitonin (PCT).

**Procedures**

The GP assessed eligibility for inclusion at the home visit. Drivers who accompanied the GPs during the home visit were equipped with portable monitoring devices (Philips Intellivue MP2 or X2) to measure blood pressure, peripheral oxygen saturation, heart rate, and respiratory rate. All vital signs and other clinical candidate predictors were registered in a case report form on site. The GP also rated the perceived likelihood of sepsis on a scale from 0–10. Either the GP or an on-call laboratory assistant obtained venous blood samples directly after inclusion. Lactate
was measured by point-of-care testing (StatStrip Xpress lactate, Nova Biomedical), as lactate cannot be measured reliably from stored blood samples.\(^{18}\) The venous blood samples were stored at \(-70^\circ C\) for later measurements of CRP and PCT. All patients received care as usual.

**Outcome definitions and assessment**

Three expert panels were created, each consisting of one GP, one emergency physician, and one intensivist (or acute care internist). These expert panels established the primary outcome: ‘sepsis within 72 hours of inclusion’, using all relevant information from medical records, per Sepsis-3 definition.\(^{19}\) The operational definition of sepsis is the presence of infection and a SOFA score\(^{20}\) at least two above the baseline. Cases were divided among the three panels, with 10% of all cases being evaluated by all three panels for inter-rater and inter-panel reliability. If panel members could not reach a consensus on the presence or absence of sepsis, the case was discussed in a face-to-face meeting until consensus was reached.

Secondary outcomes assessed by the expert panel included whether the infection was the cause of acute complaints (yes/no) and the need for hospital treatment (on a scale from 0–10). Furthermore, the presence or absence of an ‘adverse outcome’, defined as an intensive care unit (ICU) admission within 72 hours or death within 30 days of inclusion, was determined.

**Statistical analysis**

Baseline characteristics of the study population were described using the mean and standard deviation for continuous variables with a normal distribution; and the median and interquartile range (IQR) for variables with a skewed distribution. Inter-rater and inter-panel reliability were assessed using Cohen’s kappa for the primary outcome of sepsis.

Multiple imputations using multivariate imputation by chained equations (MICE) procedure\(^{21,22}\) were used to account for missing data. The regression coefficients and performance measures of the imputed datasets were pooled using Rubin’s rules\(^{23}\) and the total covariance matrix, respectively.

First, a multivariable logistic regression model was developed using all clinical parameters. Subsequently, lactate, CRP, and PCT were added to this clinical model. The linearity of the relationship between continuous variables and the log odds of sepsis was assessed. For non-linear relationships, a restricted cubic spline was used. Backward selection with \(P < 0.157\) as selection criterion (based on the Akaike information criterion)\(^{24,25}\) was used to remove any non-informative clinical parameters and biomarkers. Subsequently, performance measures of the model with and without biomarkers were compared using predictors as continuous variables (hereafter referred to as the ‘continuous model’). Variables included in this model were then dichotomised, creating a simplified model based on a simple count of the number of predictors. All cut-off points of vital signs used in NEWS were considered for the simplified model, and the model with the highest C-statistic (equal to the area under the receiver operating curve) was chosen as the final model.

Combined with previously described methods for imputing missing data and variable selection,\(^{26}\) optimism was calculated to adjust for C-statistics of the continuous models using tenfold cross-validation. The calibration slope was used as a shrinkage factor for model regression coefficients and subsequently re-estimating the intercept.

Discrimination was evaluated using the C-statistic. Calibration was assessed by visual inspection of the calibration plots and by evaluating the calibration slope and Brier score. In addition, the calibration of external datasets was also assessed using the observed-to-expected (O/E) ratio as a measure for mean calibration. Percentiles of bootstrapped samples were used to calculate 95% confidence intervals (CIs) for performance measures. Performance measures of the continuous and simplified model were compared to each other, as well as to the performance of existing scoring systems, that is, SIRS, qSOFA, and NEWS.
Table 1. Patient characteristics by sepsis diagnosis, N = 357

| Characteristic                      | Patients with sepsis (n = 151) | Patients without sepsis (n = 206) |
|-------------------------------------|---------------------------------|-----------------------------------|
| **Demographics**                    |                                 |                                   |
| Age, years, median (IQR)           | 80 (74–85)                      | 79 (68–86)                        |
| Sex, n(%)                          |                                 |                                   |
| Male                                | 93 (62)                         | 123 (60)                          |
| Female                              | 58 (38)                         | 83 (40)                           |
| **Comorbidities, n(%)**             |                                 |                                   |
| Diabetes                            | 55 (36)                         | 49 (24)                           |
| COPD                                | 22 (15)                         | 40 (19)                           |
| Cardiac disease                     | 63 (42)                         | 59 (29)                           |
| Cerebrovascular accident            | 30 (20)                         | 39 (19)                           |
| Malignancy                          | 19 (13)                         | 30 (15)                           |
| Chronic kidney disease              | 43 (28)                         | 49 (24)                           |
| Dementia                            | 25 (17)                         | 18 (8.7)                          |
| Immunosuppressive use               | 6 (4.0)                         | 7 (3.4)                           |
| **Final diagnosis, n(%)**           |                                 |                                   |
| Respiratory tract infection         | 61 (40)                         | 74 (36)                           |
| Urinary tract infection             | 45 (30)                         | 47 (23)                           |
| Abdominal infection                 | 12 (7.9)                        | 7 (3.4)                           |
| Skin/soft tissue infection          | 11 (7.3)                        | 17 (8.3)                          |
| Infection with unknown source       | 11 (7.3)                        | 25 (12)                           |
| Other source of infection           | 11 (7.3)                        | 8 (3.9)                           |
| Non-infectious diagnosis            | —                               | 28 (14)                           |
| **Candidate predictors**            |                                 |                                   |
| Tyramin temperature, °C, mean (SD)  | 39.0 (0.7)                      | 38.5 (1.0)                        |
| Systolic blood pressure, mmHg, mean (SD)  | 135 (25)                      | 139 (24)                          |
| Heart rate, beats/min, mean (SD)    | 100 (20)                        | 94 (20)                           |
| Respiratory rate, breaths/min, mean (SD)  | 26 (6)                        | 23 (7)                            |
| Peripheral oxygen saturation, %, median (IQR) | 93 (90–95)                  | 95 (93–97)                        |
| Altered mental status, n(%)         | 81 (54)                         | 46 (22)                           |
| Rigors, n(%)                        | 100 (66)                        | 123 (60)                          |
| Rapid illness progression, yes, n(%) | 127 (84)                      | 144 (70)                          |
| Lactate, mmol/L, median (IQR)       | 1.6 (1.1–2.1)                   | 1.3 (0.9–1.7)                     |
| C-reactive protein, mg/L, median (IQR)  | 85 (34–145)                  | 57 (20–114)                       |
| Procalcitonin, ng/mL, median (IQR)  | 0.25 (0.09–1.20)               | 0.08 (0.03–0.22)                  |
| Time to blood collection, minutes, median (IQR) | 50 (26–65)                  | 45 (15–65)                        |
| **Secondary outcomes, n(%)**        |                                 |                                   |
| Hospital admission                  | 134 (89)                        | 76 (37)                           |
| Length of stay, days, median (IQR)  | 5.2 (3.1–8.3)                   | 4.5 (2.5–6.5)                     |
| ICU admission within 72 hours       | 11 (7.3)                        | 1 (0.5)                           |
| 30-day mortality                    | 13 (8.6)                        | 8 (3.9)                           |

*Missing n = 1, *Missing n = 2, *Missing n = 6, *Missing n = 13. COPD = chronic obstructive pulmonary disease. ICU = intensive care unit. IQR = interquartile range. SD = standard deviation.

and to the likelihood of sepsis (on a scale from 0–10) according to the GP on site.

R (version 4.0.5) package was used for the analyses.

**Sensitivity analyses**

Model performance for secondary outcomes was assessed to evaluate potential incorporation bias resulting from the use of the SOFA score (by the expert panel) as part of the sepsis definition, as well as for a more conservative calculation of the SOFA score (fewer SOFA points for decreased oxygen saturation and altered mental status).

**External validation**

Datasets from patients with suspected infections assessed in two Dutch EDs were used to test the external validity of both the continuous and simplified model. The C-statistic discrimination was assessed, and the continuous and simplified models were compared with NEWS. The calibration was assessed using calibration plots, as well as mean calibration and calibration slope. A more detailed description can be found in Supplementary Appendix S1.

**RESULTS**

**Study population and outcome**

In total, 357 patients were included for analysis (Figure 1). The median age was 80 years (IQR 71–86) and 61% were male (Table 1). The GPs referred 199 patients (56%) to the ED directly after inclusion, of which 188 (94%) were subsequently admitted to hospital. Of the 158 patients not referred immediately, 22 (14%) were admitted to hospital within the first 72 hours after inclusion (data not shown). Of the 357 patients included in the analysis, 12 (3.4%) were admitted to the ICU within 72 hours after inclusion, and overall 30-day mortality was 5.6%. The proportion of missing values was low for all candidate predictors, with the highest being 3.6% for PCT. A total of 151 patients (42%) had sepsis, according to the expert panel. Cohen’s kappa, indicating the inter-rater reliability between members within the same panel, ranged between 0.57 and 0.76 (mean 0.68), and Cohen’s kappa for inter-panel reliability ranged between 0.69 and 0.95 (mean 0.79) [see Supplementary Table S1]. Table 1 shows a summary of the characteristics of patients with and without sepsis.

**Prediction model development**

Of the nine clinical candidate predictors, six were included in the continuous model after backward selection: aged ≥65 years; temperature ≥38°C; systolic blood pressure ≤110 mmHg; respiratory rate; peripheral oxygen saturation ≤95%; and mental status. Age was included as a restricted cubic spline with three knots. After correction for optimism, the continuous model maintained a C-statistic of 0.80 was identical to the C-statistic of 0.80 was identical to the C-statistic discrimination was assessed, and the continuous and simplified models were compared with NEWS. The calibration was assessed using calibration plots, as well as mean calibration and calibration slope. A more detailed description can be found in Supplementary Appendix S1.

R (version 4.0.5) package was used for the analyses.
continuous model. Analyses of individual biomarkers are shown in Supplementary Figure S1.

A simplified model was created through the dichotomisation of variables included in the continuous model (Box 1). Models without respiratory rate were also evaluated, as the respiratory rate is less feasible for GPs to perform. Heart rate showed collinearity with respiratory rate, and model performance did not decrease after substitution. Consequently, heart rate was used instead of respiratory rate in the final simplified model.

Discrimination of the simplified model (C-statistic of 0.80, 95% CI = 0.76 to 0.83) was nearly identical to the continuous model (Figure 2). Diagnostic accuracy measures for the simplified model at different cut-off scores are presented in Table 2, distribution of the patients with and without sepsis are shown in Figure 3, and predicted rate of sepsis in Figure 4. The calibration of the simplified model was also similar to the continuous model (see Supplementary Figure S2). The use of multiple cut-off points for individual variables in the model, or grouping score categories, did not significantly improve performance.

Comparison with existing models
Performance of the continuous and simplified models was compared to SIRS, qSOFA, and NEWS (Table 3). NEWS showed similar performance compared to the simplified model with a C-statistic of 0.79 (95% CI = 0.75 to 0.83). SIRS and qSOFA had lower C-statistics of 0.66 (95% CI = 0.61 to 0.70) and 0.71 (95% CI = 0.66 to 0.75), respectively (Figure 5). The perceived probability of sepsis within 72 hours by the GP on site resulted in a C-statistic of 0.73 (95% CI = 0.67 to 0.78; data not shown). Brier scores for continuous and simplified models were lower, that is, better than SIRS, qSOFA, and NEWS.

Sensitivity analyses
The prediction of secondary endpoints (including an alternative sepsis definition using more restrictive calculation of the SOFA score) resulted in comparable performance results for the continuous model, simplified model, and NEWS for all analyses. C-statistics ranged between 0.7 and 0.8 for all outcomes, except for prediction of ‘adverse outcome’ (ICU admission <72 hours or 30-day mortality), where a C-statistic of 0.58 (95% CI = 0.51 to 0.66) was found for the continuous model, compared to 0.62 (95% CI = 0.53 to 0.69) for both the simplified model and NEWS (see Supplementary Table S3).

External validation
The first validation dataset (Dataset 1) was from a teaching hospital in the south of the Netherlands and previously published by Latten et al. The population consisted of 440 patients with a median age of 71 years, of whom 163 (37%) were diagnosed with sepsis (severe sepsis or septic shock according to the Sepsis-2 definitions). A C-statistic of 0.80 (95% CI = 0.77 to 0.83) was found for the simplified model and 0.84 (95% CI = 0.80 to 0.87) for the continuous model. Calibration showed an O/E ratio of 1.4 for the simplified model and 1.5 for the continuous model.
The second dataset (Dataset 2) from an academic medical centre in the north of the Netherlands consisted of 1340 patients with a median age of 65 years, of whom 342 (26%) were diagnosed with sepsis (Sepsis-3 criteria). In this dataset, the C-statistic was 0.70 (95% CI = 0.67 to 0.72) for the simplified model and 0.70 (95% CI = 0.67 to 0.73) for the continuous model. The O/E ratio was 1.4 for the simplified model and 1.7 for the continuous model (see Supplementary Tables S4 and S5, and Supplementary Figures S3–S5 for complete external validation results).

**DISCUSSION**

**Summary**

In this observational cohort study, a new and easy-to-use prediction model was developed for the early recognition of sepsis in primary care. Biomarkers provided no significant improvement in prediction performance when added to the model. The respiratory rate could be replaced with the more accessible and more reliable measure, heart rate, without decreasing the prediction performance of the simplified model. The performance of the simplified model was significantly better than SIRS and qSOFA. The outcomes of the present study's simplified model were comparable to NEWS.

The validity of the simplified model was confirmed in the external validation, though some differences were found in discrimination and calibration compared to development data.

Three different aspects may have contributed to these discrepancies. First, the outcome ‘sepsis’ was defined differently in the external datasets. The SIRS-based sepsis definition may have introduced incorporation bias in the first external dataset (Dataset 1), resulting in better NEWS predictions. Second, the variable ‘altered mental status’ was registered differently. Any empirical change in mental status was sufficient in the presented study cohort, while a decrease in the Glasgow coma score was used in the validation cohorts. This score is probably less sensitive

| Cut-off point, (n) | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR– (95% CI) | PPV (95% CI) | NPV (95% CI) |
|-------------------|----------------------|----------------------|--------------|--------------|--------------|--------------|
| ≥1 (352) | 100 (98 to 100) | 2.4 (0.8 to 5.6) | 1.02 (1.00 to 1.05) | 0.00 | 43 (38 to 48) | 100 |
| ≥2 (324) | 99 (96 to 100) | 16 (11 to 21) | 1.18 (1.11 to 1.25) | 0.04 (0.01 to 0.31) | 46 (41 to 52) | 97 (84 to 100) |
| ≥3 (251) | 92 (87 to 96) | 46 (39 to 53) | 1.69 (1.48 to 1.93) | 0.17 (0.10 to 0.31) | 55 (49 to 62) | 89 (81 to 94) |
| ≥4 (118) | 60 (51 to 68) | 86 (81 to 91) | 4.39 (3.03 to 6.34) | 0.47 (0.38 to 0.57) | 76 (68 to 84) | 74 (68 to 80) |
| ≥5 (32) | 18 (12 to 25) | 98 (94 to 99) | 7.37 (2.90 to 18.7) | 0.84 (0.78 to 0.91) | 84 (87 to 95) | 62 (56 to 67) |

LR+ = positive likelihood ratio. LR– = negative likelihood ratio. PPV = positive predictive value. NPV = negative predictive value.

Figure 4. Predicted rate of sepsis with 95% confidence intervals for all scores on the simplified model.

Figure 5. Receiver operating curves of the simplified model, NEWS, qSOFA, and SIRS for the outcome sepsis. qSOFA = quick Sequential Organ Failure Assessment. NEWS = National Early Warning Score. SIRS = systemic inflammatory response syndrome.

Table 2. Diagnostic accuracy measures with 95% confidence intervals of the simplified prediction model for predicting sepsis at different score thresholds in development data, N = 357
to the hospital received more diagnostic tests than non-referred patients. Second, as some candidate predictors were also part of the SOFA score, this may have resulted in incorporation bias. Therefore, sensitivity analyses were performed, using a stricter calculation of the SOFA score and alternative outcomes, that is, adverse outcomes and need for hospital treatment according to the expert panel. These analyses did not suggest significant bias. Furthermore, not all eligible patients had been included in the study. However, the most common reasons not to include eligible patients were not based on patient factors but rather on having too busy a shift, which is unlikely to have resulted in selection bias. Finally, the external validations were performed in patients assessed in the accident and emergency department due to suspected infection. Ideally, validation of the model would have been performed in a primary care population in whom the decision to refer a patient to the hospital was not yet made. These data were not available to the authors. However, the fact that the model also performed well in other domains underscores robustness.

Comparison with existing literature
Other clinical prediction rules have been proposed for either patients with sepsis or those who are critically ill in the prehospital setting. These were mostly derived from retrospective data retrieved from patients transported by ambulance and used SIRS-based sepsis definitions. Only one prospective cohort study using the Sepsis-3 outcome definition was found in the prehospital setting, which included 551 patients with suspected infection in the ambulance. This study showed blood pressure $\leq 100$ mmHg, temperature $>38.5$ °C, lactate $>4$ mmol/L, gastrointestinal symptoms, and altered mental status to be most predictive of sepsis. These findings mainly align with the results of the present study and support the decision not to include respiratory rate in the simplified model. In the present data, only three patients showed lactate $>4$ mmol/L, which might explain why lactate was not found to be a useful predictor in the primary care setting. Two studies were found in which vital signs were measured in acutely ill adult patients in a primary care setting. These were mostly performed in a primary care population in whom the decision to refer a patient to the hospital was not yet made. These data were not available to the authors. However, the fact that the model also performed well in other domains underscores robustness.

**Table 3. Optimism corrected performance measures in development data of the multivariable model consisting of clinical parameters as continuous variables (continuous model), with the addition of lactate and procalcitonin (continuous model + biomarkers), simplified model, SIRS, qSOFA, and NEWS, N=357**

| Prediction model                      | C statistic (95% CI) | Calibration slope | Brier score |
|--------------------------------------|----------------------|-------------------|------------|
| Continuous model                     | 0.80 (0.75 to 0.84)  | 0.86              | 0.181      |
| Continuous model + biomarkers        | 0.80 (0.74 to 0.84)  | 0.83              | 0.174      |
| Simplified model                     | 0.80 (0.76 to 0.83)  | 1.00              | 0.175      |
| NEWS                                 | 0.79 (0.75 to 0.83)  | 1.01              | 0.182      |
| qSOFA                                | 0.71 (0.66 to 0.75)  | 1.02              | 0.207      |
| SIRS                                 | 0.66 (0.61 to 0.70)  | 1.03              | 0.224      |

qSOFA = quick Sepsis-related Organ Failure Assessment. NEWS = National Early Warning Score. SIRS = systemic inflammatory response syndrome (based on criteria: temperature $<36$ °C or $>38$ °C, respiratory rate $>20$ breaths/min, and heart rate $>90$ beats/min).

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**Ethical approval**
The study received ethical approval from the Medical Research Ethics Committee Utrecht (reference number: 18-169).
Data
De-identified patient data that underlie the presented results in this article will be made available to researchers with a methodological sound proposal. A data dictionary of all variables will be provided. Data will be available from 3 months after publication until 5 years after publication. Requests should be made to the corresponding author.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
Rogier M Hopstaken declares to have received honoraria from Lumiradx, Photondelta, and Abbott for advisory board meetings and lecturing. Arthur RH van Zanten reports receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Baxter, Cardinal Health, Danone-Nutricia, DIM3, Fresenius Kabi, Mermaid, Lyric, and Nestlé-Novartis. Theo JM Verheij participated in studies that were funded by the EU and partly by Biomerieux, Becton Dickinson, Janssen Pharmaceuticals, and Abbott (IMI projects). All other authors have declared no competing interests.

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