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Risk factors for non-invasive/invasive ventilatory support in patients with COVID-19 pneumonia: A retrospective study within a multidisciplinary approach

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ABSTRACT

Objectives: To investigate risk factors for non-invasive/invasive ventilatory support (NI/I-VS) in patients with coronavirus disease 2019 (COVID-19).
Methods: All consecutive patients admitted to the Infectious Diseases Unit and Intensive Care Unit (ICU) of Santa Maria Annunziata Hospital (Florence, Italy), from February 25 to April 25, 2020, with a confirmed COVID-19 diagnosis were enrolled in this retrospective cohort study. NI/I-VS was defined as the need for continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) (non-invasive ventilation) or mechanical ventilation, not including low-flow systems of oxygen therapy such as the Venturi mask or nasal cannula.
Results: Ninety-seven patients were enrolled; 61.9% (60/97) were male and the median patient age was 64 years. The in-hospital mortality was 9.3%. Thirty-five of the 97 patients (36%) required ICU admission and 94.8% (92/97) were prescribed oxygen therapy: 10.8% (10/92) by nasal cannula, 44.5% (41/92) by Venturi mask, 31.5% (29/92) by CPAP, 2.2% (2/92) by BPAP, and 10.8% (10/92) by mechanical ventilation following intubation. On univariate analysis, patients with a body mass index >30, type II diabetes mellitus, and those presenting with dyspnoea, asthenia, SOFA score ≥2 points, PaO_2/FiO_2 <300, temperature >38 °C, increased levels of lactate dehydrogenase (LDH), alanine aminotransferase, and C-reactive protein, and a D-dimer >1000 ng/mL at admission more frequently underwent NI/I-VS. Multivariate logistic regression analysis confirmed temperature >38 °C (odds ratio (OR) 21.2, 95% confidential interval (95% CI) 3.5–124.5, $p = 0.001$), LDH >250 U/l (OR 15.2, 95% CI 1.8–128.8, $p = 0.012$), and D-dimer >1000 ng/mL (OR 4.5, 95% CI 1.2–17.3, $p = 0.027$) as significantly associated with the requirement for NI/I-VS. A non-significant trend ($p = 0.051$) was described for PaO_2/FiO_2 <300.
Conclusions: Temperature >38 °C, LDH > 250 U/l, and D-dimer >1000 ng/mL were found to be independent risk factors for NI/I-VS in COVID-19 patients. In order to quickly identify patients likely at risk of developing a critical illness, inflammatory markers should be assessed upon hospital admission.

Introduction

In December 2019, a novel coronavirus disease appeared in Wuhan (China) and spread rapidly worldwide, leading to a pandemic scenario (Zhu et al., 2020). The infection caused by the novel coronavirus was named coronavirus disease 2019

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(COVID-19), and this coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) (Anon, 2020a).

As of May 13, 2020, the WHO had reported 4,170,424 confirmed COVID-19 cases globally, with an average mortality of 6.89%, while in Italy, on the same date, 221,133 confirmed COVID-19 cases had been diagnosed, with an average mortality of 13.35% (Anon, 2020b; Anon, 2020c).

SARS-CoV-2 causes a wide spectrum of clinical manifestations; most patients develop a short-lasting mild clinical illness; however, in contrast, a small percentage of patients suffer a severe disease, including manifestations of acute respiratory distress syndrome (ARDS) (Guan et al., 2020a).

Facing a life-threatening infection, the recognition of reliable risk factors is warranted in order to guarantee a fast and appropriate medical response.

Methods

Setting and study period

The study was conducted at Santa Maria Annunziata Hospital, a medium-size hospital with 300 beds in the southern area of Florence, Italy.

This was a retrospective, single-centre, observational cohort study. All consecutive adult patients presenting to the emergency department (ED) between February 25 and April 25, 2020 (60 days) and admitted to the Infectious Diseases Unit (IDU) or to the Intensive Care Unit (ICU) with a confirmed diagnosis of COVID-19, were included. The diagnosis of COVID-19 was confirmed by positive result on real-time reverse transcriptase PCR (RT-PCR) for SARS-CoV-2 on nasal and pharyngeal swab specimens.

Patient management

A multidisciplinary approach between the IDU and ICU specialists was employed from the beginning of the study period: three meetings per day were held in order to share patient management information, especially supportive treatments such as ventilatory support, experimental drugs, and the administration of antiviral and antibiotic medications.

Treatments, including the use of antivirals, antibiotics, immunomodulating agents (corticosteroids and tocilizumab), and ventilatory support, were administered following local guidelines based on the best available evidence at that time and consistent with the 'Vademecum' realized by the Lombardy Region section of the Italian Society of Infectious and Tropical Diseases (SIMIT Lombardia) (Anon, 2020d). Tocilizumab was administered according to and in the context of the Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) clinical trial (NCT04317092) (Anon, 2020e).

Non-invasive/invasive-ventilatory support (NI/I-VS) was defined as the need for continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) (non-invasive ventilation) or mechanical ventilation, not including low-flow systems oxygen therapy such as the Venturi mask or nasal cannula.

Data collection

Data were obtained from the patient electronic medical records and were reviewed by a trained team of five physicians (three IDU and two ICU specialists) and one IDU nurse. They included baseline characteristics, clinical features, including symptoms history and Sequential Organ Failure Assessment (SOFA) (Vincent et al., 1996), the findings of laboratory tests performed upon arrival in the ED, chest radiography, admission ward (IDU or ICU), supplemental oxygen requirement and type of administration during the in-hospital stay, antiretroviral therapy (lopinavir/ritonavir or darunavir based drugs), hydroxychloroquine, antibiotic therapy, and immunomodulating therapy with corticosteroids or tocilizumab. Baseline characteristics were the following: sex, age, community or healthcare-acquired infection (including patients working as healthcare workers and patients living in long-term care facilities), body mass index (BMI, kg/m^2), comorbidities such as chronic obstructive pulmonary disease (COPD; including asthma), obesity (BMI > 30), diabetes, coronary heart disease, hypertension, cerebrovascular disease (including dementia), active malignancy (solid or haematological), HIV, other immunodeficiency (immunosuppressive treatment at the admission), chronic renal failure (according to the "Kidney Disease: Improving Global Outcomes" clinical practice guidelines) (Levey et al., 2005). The Charlson comorbidity index (CCI) score was calculated for each patient (Charlson et al., 1987).

Study outcomes

The primary aim was to investigate the risk factors for NI/I-VS, defined as the need for CPAP or BPAP (non-invasive ventilation) or mechanical ventilation, excluding low-flow oxygen support, such as Venturi mask or nasal cannula use.

Statistical analysis

Continuous variables were presented as the median with interquartile range (IQR) and the maximum–minimum values; these were dichotomized where appropriate. Categorical variables were reported as percentages and compared using the Chi–square test. Fisher's exact test was also used to estimate continuous variables if one set contained fewer than five expected subjects. The Mann–Whitney *U*-test was used to study non-parametric continuous variables (median). Logistic regression was performed to explore the risk factors associated with the primary outcome. All variables associated with the primary outcome in the univariate model with $p < 0.05$ were entered into a backward-logistic multivariate regression model. Considering the total number of events ($n = 41$) in this study and to avoid overfitting the model, four variables were chosen for multivariable analysis on the basis of previous findings and clinical constraints. Interactions in the model that were significant were tested in a stratified analysis, and the odds ratio (OR) with 95% confidence intervals (95% CI) were calculated. A value of $p < 0.05$ was considered statistically significant. The statistical analysis was conducted using IBM SPSS Statistics version 23.0 software (IBM Corp., Armonk, NY, USA).

Table 1
Demographic, clinical, and laboratory findings on admission, treatment received, and outcome.

	Total (n = 97)	Low-flow oxygen support group[a] (n = 56)	Non-invasive/invasive ventilatory support group[b] (n = 41)	p-Value
Baseline characteristics				
Age (years), median (IQR)	64 (54.5–75)	64.5 (53–78)	63 (57.5–72.5)	0.441
Sex, male	60 (61.9%)	31 (55.4%)	29 (70.7%)	0.124
CCI score, median (IQR)	3 (0–4)	2.5 (0–4.75)	3 (1–4)	0.434
CCI score >3	51 (52.6%)	28 (50%)	23 (56.1%)	0.552
Obesity (BMI > 30 kg/m^2)	21 (21.6%)	6 (10.7%)	15 (36.6%)	0.002*
BMI (kg/m^2), median (IQR)	25.7 (23.9–28.1)	24.9 (22.6–26.5)	27.5 (25–31.6)	<0.001*
Diabetes	15 (15.5%)	4 (7.1%)	11 (26.8%)	0.01*
COPD (including asthma)	10 (10.3%)	3 (5.4%)	7 (17.1%)	0.090
Coronary artery disease	8 (8.2%)	4 (7.1%)	4 (7.1%)	0.718
Hypertension	48 (49.5%)	27 (48.2%)	21 (51.2%)	0.770
Cerebrovascular disease (including vascular dementia)	12 (12.4%)	8 (14.3%)	4 (7.1%)	0.551
Active neoplasia (solid or onco-haematological)	2 (2.1%)	2 (3.6%)	0 (0)	0.500
HIV infection	0 (0)	0 (0)	0 (0)	–
Other immunodeficiency	2 (2.1%)	1 (1.8%)	1 (1.8%)	1
Chronic renal failure	5 (5.2%)	2 (3.6%)	3 (5.4%)	0.647
Symptoms at home				
Fever (>37.5 °C)	85 (87.6%)	51 (91.1%)	34 (82.9%)	0.229
Cough	68 (70.1%)	40 (71.4%)	28 (68.3%)	0.739
Pharyngodynia	8 (8.2%)	6 (10.7%)	2 (4.9%)	0.461
Dyspnoea	43 (44.3%)	20 (35.7%)	23 (56.1%)	0.046*
Haemoptysis	1 (1%)	0 (0)	1 (1.8%)	0.423
Headache	2 (2.1%)	1 (1.8%)	1 (1.8%)	1
Coryza	3 (3.1%)	1 (1.8%)	2 (4.9%)	0.572
Diarrhoea	4 (4.1%)	1 (1.8%)	3 (5.4%)	0.308
Myalgia	8 (8.2%)	4 (7.1%)	4 (7.1%)	0.719
Asthenia	28 (28.9%)	7 (12.5%)	21 (51.2%)	<0.001*
Vomiting	4 (4.1%)	2 (3.6%)	2 (4.9%)	1
Rash	1 (1%)	1 (1.8%)	0 (0)	1
Time since symptoms to admission (days), median (IQR)	6 (3–9)	6 (2–8)	6 (4–9.5)	0.080
Clinical features, imaging and laboratory findings on admission				
Temperature >38 °C	25 (25.8%)	5 (8.9%)	20 (48.8%)	<0.001*
SOFA score at admission, median (IQR)	2 (1–2)	1 (1–2)	2 (2–3)	<0.001*
SOFA score ≥2	58 (59.8%)	24 (42.9%)	34 (82.9%)	<0.001*
PaO_2/FiO_2, median (IQR)	296 (244–348)	318 (272–379)	261 (200–299)	<0.001*
PaO_2/FiO_2 <300	54 (55.7%)	21 (37.5%)	33 (80.5%)	<0.001*
Infiltrates on chest imaging[c]	88 (90.7%)	48 (85.7%)	40 (97.6%)	0.080
Leukocytes ($\times 10^9$/l), median (IQR)	5.7 (4.6–8.8)	5.3 (4.5–7.8)	6.3 (4.6–8.4)	0.303
Leukocytes <4 × 10^9/l	17 (17.5%)	9 (16.1%)	8 (19.5%)	0.660
Leukocytes >10 × 10^9/l	16 (16.5%)	9 (16.1%)	7 (17.1%)	0.896
Lymphocytes ($\times 10^9$/l), median (IQR)	0.90 (0.7–1.2)	1 (0.7–1.2)	0.85 (0.71–1.34)	0.509
Lymphocytes <0.8 × 10^9/l	35 (36.1%)	17 (30.4%)	18 (43.9%)	0.170
Platelets ($\times 10^9$/l), median (IQR)	180 (149.5–249.5)	172 (148–242)	187 (149–262)	0.537
Platelets <150 × 10^9/l	24 (24.7%)	14 (25%)	10 (24.4%)	0.945
ALT (U/l), median (IQR)	31 (21–42)	24 (16–38)	39 (26.5–50)	<0.001*
ALT >40 U/l	30 (30.9%)	11 (19.6%)	19 (46.3%)	0.006*
LDH (U/l), median (IQR)	319.5 (234–402)	270.5 (210–362)	370.5 (295.5–477.5)	<0.001*
LDH > 250 U/l	64 (66%)	29 (51.8%)	35 (85.4%)	<0.001*
Creatinine (mg/dl), median (IQR)	0.92 (0.7–1)	0.92 (0.7–1)	0.91 (0.7–1.1)	0.540
D-dimer (ng/mL), median (IQR)	923 (612–1346)	992 (804–1433)	948.5 (700–1202)	0.776
D-dimer >1000 ng/mL	35 (43.8%)	12 (21.4%)	23 (56.1%)	0.005*
CRP (mg/dl), median (IQR)	7.4 (3–13)	6 (2–9)	12 (5–19)	<0.001*
Procalcitonin (ng/mL), median (IQR) (n = 62)	0.13 (0.07–0.3)	0.10 (0.06–0.27)	0.16 (0.09–0.30)	0.155
Therapy				
Antiviral	89 (91.8%)	49 (87.5%)	40 (97.6%)	0.075
Hydroxychloroquine	88 (90.7%)	48 (85.7%)	40 (97.6%)	0.045*
Corticosteroids	44 (45.4%)	14 (25%)	30 (73.2%)	<0.0001*
Tocilizumab	24 (24.7%)	3 (5.4%)	21 (51.2%)	<0.0001*
Antibiotic	91 (93.8%)	50 (89.3%)	41 (100%)	0.037*
Clinical course (on May 14, 2020)				
Cured and discharged	86 (88.7%)	53 (94.6%)	33 (80.5%)	0.034
Still admitted	2 (2.1%)	1 (1.8%)	1 (1.8%)	–
Died	9 (9.3%)	2 (3.6%)	7 (17.1%)	–

ALT, alanine aminotransferase; BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; SOFA, Sequential Organ Failure Assessment.

[a] Low-flow oxygen support group: Venturi mask or low-flow systems oxygen therapy (nasal cannula). This group included five patients (8%) with no need for supplemental oxygen.

[b] Non-invasive/invasive ventilatory support group: continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) (non-invasive ventilation) or mechanical ventilation.

[c] Including chest X-ray and computed tomography scan.

Table 2
Univariate analysis and multivariate logistic regression assessing risk factors for non-invasive/invasive ventilatory support.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Baseline characteristics				
Male sex	1.94 (0.82–4.58)	0.126		
Age (years)	0.99 (0.97–1.02)	0.817		
CCI score >3	1.27 (0.56–2.87)	0.552		
Obesity (BMI > 30 kg/m^2)	4.80 (1.66–13.85)	0.004	4.18 (0.61–28.48)	0.144
Diabetes	4.76 (1.39–16.29)	0.013	2.27 (0.21–24.47)	0.497
COPD (including asthma)	3.63 (0.88–15.03)	0.075		
Coronary artery disease	0.71 (0.16–3.02)	0.645		
Hypertension	1.12 (0.50–2.52)	0.770		
Cerebrovascular disease (including vascular dementia)	0.65 (0.18–2.32	0.506		
Chronic renal failure	2.13 (0.34–13.37)	0.419		
Symptoms at home				
Fever (>37.5 °C)	0.47 (0.14–1.62)	0.236		
Cough	0.86 (0.35–2.07)	0.739		
Dyspnoea	2.30 (1.01–5.24)	0.048	1.35 (0.32–5.71)	0.677
Asthenia	7.35 (2.71–20.00)	<0.001	11.7 (1.02–102.34)	0.070
Clinical features, imaging and laboratory findings on admission				
Temperature >38 °C	9.71 (3.22–29.29)	<0.001	21.2 (3.5–124.5)	0.001
SOFA score ≥2	6.47 (2.45–17.09)	<0.001	6.89 (0.50–90.2)	0.149
PaO_2/FiO_2 <300	6.87 (2.67–17.65)	<0.001	4.7 (0.99–22.4)	0.051
Leukocytes <4 × 10^9/l	1.26 (0.44–3.62)	0.660		
Leukocytes >10 × 10^9/l	1.07 (0.36–3.17)	0.896		
Lymphocytes <0.8 × 10^9/l	1.79 (0.77–4.15)	0.172		
Platelets <150 × 10^9/l	0.96 (0.38–2.46)	0.945		
ALT >40 U/l	3.45 (1.40–8.51)	0.007	10.42 (0.74–146.5)	0.82
LDH > 250 U/l	10.05 (2.75–36.71)	<0.001	15.2 (1.8–128.8)	0.012
Creatinine (mg/dl), median	1.04 (0.40–2.67)	0.934		
D-dimer >1000 ng/mL	3.90 (1.48–10.24)	0.006	4.5 (1.2–17.3)	0.027
CRP (mg/dl), median	1.12 (1.03–1.20)	0.003	1.48 (0.42–15.4)	0.950
Procalcitonin (ng/mL), median	2.43 (0.83–7.08)	0.103		

ALT, alanine aminotransferase; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LDH, lactate dehydrogenase; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

Results

A total of 97 COVID-19 patients were eligible for the study and their main characteristics are reported in Table 1. Sixty (61.9%) were male. The median age was 64 years (IQR 54.5–75, range 25–99 years), and females were significantly older, presenting a median age of 75 years (IQR 58–81.5, range 22–99 years) ($p = 0.009$).

An exposure history was reported for 11 (16.5%) patients from long-term care facilities, three (3.1%) patients had nosocomial transmission, and three (3.1%) were healthcare workers.

Comorbidities were present in nearly 60% of patients, with hypertension being the most common one, followed by type II diabetes mellitus, cerebrovascular disease (including vascular dementia), and COPD. In addition to this, 21 (21.6%) had a BMI > 30. The most common symptoms before admission were fever, cough, dyspnoea, and asthenia.

At ED presentation, 58 (59.8%) patients had a SOFA score ≥2 points and 54 (55.7%) had a PaO_2/FiO_2 index <300. Increased lactate dehydrogenase (LDH) occurred in 64 (66%) patients, while 35 (36.1%) had a D-dimer >1000 ng/mL.

Thirty-five (36%) patients required ICU admission and 92 (94.8%) were prescribed a supplemental oxygen therapy: 10/92 (10.8%) with low-flow systems (nasal cannulae), 41/92 (44.5%) with a Venturi mask, 29/92 (31.5%) CPAP, 2/92 (2.2%) BPAP, and 10/92 (10.8%) underwent intubation for mechanical ventilation within 48 h of ED admission.

Eighty-nine (91.8%) patients received antivirals and 91 (93.8%) were prescribed an antibiotic therapy. Tocilizumab was administered to 24 (24.7%) of the patients, while corticosteroids were given to 44 (45.4%). All patients received anticoagulant prophylaxis with standardized doses of low molecular weight heparin.

As of May 14, 2020, 86 (88.7%) patients had been cured and discharged from the hospital, two (2.1%) were still in the hospital with an improving condition, while nine (9.3%) had died. Specifically two (3.6%) of the 56 patients not in the NI/I-VS group died, likely due to sudden cardiac death, and seven (17.1%) of the 41 patients in the NI/I-VS group died.

On univariate analysis, a BMI > 30, diabetes, history of dyspnoea or asthenia, SOFA score (at admission) ≥2 point, PaO_2/FiO_2 index (at admission) lower than 300, temperature (at admission) >38 °C, increased LDH, increased alanine aminotransferase, increased C-reactive protein, and a D-dimer >1000 ng/mL were significantly associated with non-invasive/invasive ventilatory support.

The 75 patients with complete data for all variables were included in the multivariate backward-logistic regression model. On multivariate analysis, temperature >38 °C, LDH > 250 U/l, and D-dimer >1000 ng/mL were significantly associated with the requirement for non-invasive/invasive ventilatory support, while a PaO_2/FiO_2 <300 showed a tendency towards a significant association (Table 2).

Discussion

In this cohort study, the clinical characteristics of hospitalized COVID-19 patients were analysed in order to highlight possible risk factors associated with the requirement for non-invasive/invasive ventilatory support. Baseline characteristics were found to be similar to those reported in the largest Italian study available to date, performed by Grasselli et al. (2020): a higher prevalence of males, median age of 64 years, and the presentation of the common comorbidities hypertension and diabetes. In contrast, however, only 10% of patients in the present study suffered from cardiovascular disease. Similar baseline data have been reported previously in two studies from China (Wang et al., 2020; Guan et al., 2020b) and, more recently, by Richardson et al. (2020) in New York, USA.

On the other hand, older age, in the present study, was not associated with a complicated course requiring intensive ventilatory support. As suggested by Grasselli et al. (2020), the median age (63 years) of the hospitalized patient is comparable to the median age of the total Italian COVID-19 cases (Anon, 2020c). As a consequence, it could barely be associated with a poorer outcome as a unique risk factor.

As shown in the case-series studies reported by Bhatraju et al. (2020) in the USA and by Simonnet et al. (2020), obesity seemed to be associated with severe COVID-19 illness. In the present study population, 15 (71.4%) out of 21 patients with a BMI > 30 received intensive ventilatory support (four mechanical ventilation and 11 non-invasive ventilation). Nevertheless, obesity did not reach the significance threshold in the multivariate analysis in this study.

Moreover, focusing on patient clinical features and laboratory findings at admission, it was found that fever and increased levels of LDH and D-dimer were independently associated with a higher intensity cure need; these findings are consistent with those of previously published studies by Zhou et al. (2020) and Wu et al. (2020).

This report appears to be one of the first case-series from Italy describing a real-life experience from a joint IDU–ICU perspective. The analysis confirmed the role as risk factors of fever and increased levels of D-dimer and LDH. These could be used as proxy markers of the hyperinflammation stage that might lead to difficult-to-treat critical illness. An early inflammatory screening should be provided upon arrival in the ED in order to stratify the illness severity.

This study has several limitations. First, the retrospective design and the non-standardized documentation available could have led to a major selection bias. Second, the modest sample size could have influenced the risk factors assessment. Finally, the data in this study came entirely from a single centre and this could potentially limit the generalizability of the findings.

In conclusion, it was found that fever (temperature >38 °C), LDH > 250 U/l, and D-dimer >1000 ng/mL were significantly associated with the requirement for non-invasive/invasive ventilatory support. Inflammatory markers screening could be useful to quickly identify patients more likely to develop a severe illness and to appropriately manage treatment.

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Ethical approval

Due to the observational and retrospective nature of the study, the need for specific informed consent from individual patients was waived. An informed consent to the treatment of personal data–usual and mandatory practice upon on hospital admission–was acquired directly from the patients or their legal representatives.

Conflict of interest

CP has received funds for speaking at symposia on behalf of Zambon, Angelini, and MSD. PB has participated on the board of and has received funds for speaking at symposia on behalf of Abbvie, MSD, Gilead, and ViiV. The authors declare no competing interests.

Author contributions

All authors made substantial contributions to this work and approved the final manuscript. LRS, CP, and SE contributed equally to this work. Concept and design: LRS, CP. Acquisition of data: LRS, CP, SE, FB, ES, ET, MP, CS, MC, RP, TM. Analysis: LRS. Writing original draft: LRS, CP. Writing review and editing: SE, MP, CS, AB, FCF, VP, PB. Supervision: FCF, VP, PB.

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