The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative agent of coronavirus disease 2019 (COVID-19), has spread worldwide, becoming a pandemic of historic dimensions. The clinical spectrum of COVID-19 ranges from asymptomatic disease to pneumonia, life-threatening complications, and, ultimately, death. Despite most infected individuals develop solely a mild illness, the mortality rate for severe cases is as high as that caused by other etiologies of severe community-acquired pneumonia.

For coping with the best clinical attention to COVID-19 patients it is crucial to perform prognosis estimations at the first clinical evaluation, offering personalized attention based on early and easily detectable predictors that support decision making, guide level of care, and optimize the allocation of health resources. Different studies have already addressed this issue, identifying clinical signs and several biomarkers as predictors of unfavorable outcome.

In this regard, different studies have addressed the possible association between the viral load in nasopharyngeal (NP) swabs and the clinical outcomes. Some studies have reported that a high number of virus copies in NP swabs, mainly defined as a cycle threshold (Ct) < 25 or < 22 in the real-time polymerase chain reaction (RT-PCR), was an independent risk factor for intubation and/or death. However, other studies have not found independent association between low Ct values and critical care admission or death. In short, the real impact of the viral load in nasopharyngeal swabs on the clinical outcomes of COVID-19 patients remains uncertain.
of initial SARS-CoV-2 viral load in NP swabs on COVID-19 patients' outcomes is not been fully elucidated, and this issue remains controversial\(^14\).

In the present prospective study on adult COVID-19 patients, stratified into mild disease (attended as outpatients) and hospital admitted with moderate or severe disease, we analyzed if the viral load of SARS-CoV-2 in NP swabs was associated with the disease severity, and the ability of NP SARS-CoV-2 viral load at the first hospital evaluation to predict unfavorable outcomes.

**Results**

Demographics, clinical characteristics, and outcome. The cohort included 321 adult patients, with the first evaluation at the Emergency room. Fifty-six (17.4\%) patients had a mild disease and were discharged after the first evaluation, and subsequently attended as outpatients until the end of follow-up; 180 (56.1\%) had a moderate course, being hospitalized in general wards, and with full recovery and hospital discharged; and 85 (26.5\%) patients were categorized as severe COVID-19 because of required admission to the ICU (32 patients [10.0\%]), in-hospital death (40 [12.5\%]), or both (13 [4.0\%]).

Demographics, symptoms, and signs of the total cohort and the three categories of disease severity are shown in Table 1. In the total cohort, males accounted for 169 (52.6\%), median age was 63 (IQR 52–77) years, and 36.8\% were ≥ 70 years old. The most common symptoms were fever (73.8\%), cough (67.3\%), and dyspnea (45.8\%). Two

| Table 1. Demographics, comorbidities, and clinical data of 321 patients with COVID-19 stratified according to disease severity. *Chronic obstructive pulmonary disease, obstructive sleep apnea, or asthma. ‡Active solid or hematologic malignant neoplasms. ‡Across all three groups. | Total cohort (n = 321) | Mild disease (n = 56) | Moderate disease (n = 180) | Severe disease (n = 85) | p value<sup>c</sup> |
|---|---|---|---|---|---|
| **Demographics, clinical characteristics, and outcome.** The cohort included 321 adult patients, with the first evaluation at the Emergency room. Fifty-six (17.4\%) patients had a mild disease and were discharged after the first evaluation, and subsequently attended as outpatients until the end of follow-up; 180 (56.1\%) had a moderate course, being hospitalized in general wards, and with full recovery and hospital discharged; and 85 (26.5\%) patients were categorized as severe COVID-19 because of required admission to the ICU (32 patients \([10.0\%]\)), in-hospital death \((40 \,[12.5\%])\), or both \((13 \,[4.0\%])\). Demographics, symptoms, and signs of the total cohort and the three categories of disease severity are shown in Table 1. In the total cohort, males accounted for 169 (52.6\%), median age was 63 (IQR 52–77) years, and 36.8\% were ≥ 70 years old. The most common symptoms were fever (73.8\%), cough (67.3\%), and dyspnea (45.8\%). Two |  |  |  |  | <sup>c</sup> |
hundred twenty-four (69.8%) patients had chest X-ray infiltrates at first hospital evaluation: 16.1% within the mild group, 77.8% in the moderate one, and 88.2% in the severe group (p < 0.001). During the follow-up, 100% of the patients in the moderate and severe groups showed pulmonary infiltrates in the evolutive chest X-ray after hospital admission. Between-group differences regarding baseline laboratory values were also identified and are detailed in Table 2.

Seventy-eight (24.3%) patients required respiratory support with high flow therapy or non-invasive mechanical ventilation, which was more frequent in patients with severe than with moderate disease (55 [64.7%] vs. 23 [12.8%], respectively, being p = 0.001). Twenty-eight (32.9%) patients, all admitted to ICU, required invasive mechanical ventilation.

Median NP viral load at first hospital evaluation was not different among the mild, moderate, or severe groups according to their clinical outcomes (Table 2). However, we found higher frequencies of NP viral load above the first tertile, the 50th percentile, and the second tertile in the severe group when comparing the three groups (p = 0.01).

We also analyzed the possible differences among demographics, chronic underlying diseases, and the days from symptoms onset to diagnosis according to the SARS-CoV-2 viral load (Table 3). Although the median days from symptoms onset to diagnosis was lower in the group with higher SARS-CoV-2 viral load (2nd vs. 1st tertile) this difference was not significant. Additionally, we performed a linear regression analysis which did not show association between both variables (p = 0.389). The only significant differences (p < 0.05) were found for the frequency of cardiovascular diseases and age ≥ 70 years. Finally, we made a linear regression analysis between the SARS-CoV-2 viral load and age, finding a significant correlation between both variables (p < 0.001) though not clinically relevant (adjusted R² 0.036).

**Table 2.** Laboratory values and nasopharyngeal SARS-CoV-2 viral load of 321 patients with COVID-19 stratified according to disease severity. aValues were available in 293 and 276 patients for CRP and D-dimer, respectively. bAcross all three groups.

|                       | Total cohort (n = 321) | Mild disease (n = 56) | Moderate disease (n = 180) | Severe disease (n = 85) | p valueb |
|-----------------------|-----------------------|----------------------|---------------------------|------------------------|----------|
| Blood counts, median (IQR) |                       |                      |                           |                        |          |
| WBC × 10⁹/µL          | 6.5 (4.7–9.0)         | 5.0 (4.0–7.0)        | 6.5 (4.8–8.7)             | 8.1 (5.3–11.7)         | < 0.001  |
| Neutrophils × 10⁹/µL  | 4.7 (3.2–7.1)         | 3.4 (2.4–4.7)        | 4.6 (3.2–6.7)             | 6.9 (4.0–9.9)          | 0.64     |
| Lymphocytes × 10⁹/µL  | 1.1 (0.8–1.6)         | 1.3 (1.1–1.6)        | 1.1 (0.8–1.6)             | .9 (0.6–1.4)           | < 0.001  |
| Platelets × 10⁹/µL    | 198 (163–257)         | 202 (164–243)        | 197 (165–253)             | 200 (161–268)          | 0.70     |
| Blood counts (categorized, %) |                       |                      |                           |                        |          |
| WBC > 11 × 10⁹/µL     | 42 (13.1)             | 1 (1.8)              | 16 (8.9)                  | 25 (29.4)              | < 0.001  |
| Neutrophils > 7.5 × 10⁹/µL | 65 (20.2)          | 0 (0)                | 31 (17.2)                 | 34 (40.0)              | < 0.001  |
| Lymphocytes < 1 × 10⁹/µL | 125 (38.9)           | 7 (12.5)             | 68 (37.8)                 | 50 (58.8)              | < 0.001  |
| Platelets < 130 × 10⁹/µL | 26 (8.1)             | 5 (8.9)              | 11 (6.1)                  | 10 (11.8)              | 0.28     |
| Biochemistry and inflammatory biomarkers, median (IQR) |                       |                      |                           |                        |          |
| Creatinine mg/dL      | .9 (.7–1.2)           | .8 (.7–1.0)          | .9 (.7–1.1)               | 1.1 (.8–1.6)           | 0.42     |
| AST U/L               | 29 (22–49)            | 24 (18–32)           | 27 (21–46)                | 39 (28–64)             | 0.01     |
| LDH U/L               | 309 (231–415)         | 222 (185–280)        | 293 (229–376)             | 400 (319–502)          | < 0.001  |
| CRP mg/La              | 57.0 (20.8–136.6)     | 16.0 (5.8–33.9)      | 53.0 (20.0–113.8)         | 142.5 (67.2–252.0)     | < 0.001  |
| D-dimer ng/mLa         | 770 (463–1608)        | 515 (345–755)        | 730 (428–1578)            | 1145 (708–2453)        | 0.07     |
| Biochemistry and inflammatory biomarkers (categorized, %) |                       |                      |                           |                        |          |
| Creatinine > 1.3 mg/dL | 60 (18.7)             | 4 (7.1)              | 28 (15.6)                 | 28 (32.9)              | < 0.001  |
| AST > 30 U/L           | 124 (38.6)            | 11 (19.6)            | 62 (34.4)                 | 51 (60.0)              | < 0.001  |
| LDH > 300 U/L          | 145 (45.2)            | 4 (7.1)              | 79 (43.9)                 | 62 (72.9)              | < 0.001  |
| CRP > 100 mg/La        | 102 (31.8)            | 1 (1.8)              | 52 (28.9)                 | 49 (57.6)              | < 0.001  |
| D-dimer > 600 ng/mLa   | 171 (53.3)            | 13 (23.2)            | 97 (53.9)                 | 61 (71.8)              | < 0.001  |
| Nasopharyngeal viral load (log10 copies/mL, median [IQR]) |                       |                      |                           |                        |          |
| Viral load (VL)        | 7.35 (5.85–8.80)      | 6.44 (4.70–8.32)     | 7.10 (5.92–8.66)          | 8.18 (6.31–8.90)       | 0.88     |
| VL ≥ 6.33 (1st tertile, %) | 215 (67.0)          | 29 (51.8)            | 122 (67.8)                | 64 (75.3)              | 0.01     |
| VL ≥ 7.35 (50th percentile, %) | 163 (50.8)         | 24 (42.9)            | 84 (46.7)                 | 55 (64.7)              | 0.01     |
| VL ≥ 8.27 (2nd tertile, %) | 107 (33.3)           | 16 (28.6)            | 52 (28.9)                 | 39 (45.9)              | 0.02     |

**Predictors of unfavorable outcome.** Twenty-three categorical variables at first hospital evaluation were identified as baseline risk factors for unfavorable outcome (admission to ICU or death) in the unadjusted logistic regression analysis: advanced age, arterial hypertension, cardiovascular disease, cancer, dyspnea, higher temperature and respiratory rate, lower diastolic blood pressure and capillary oxygen saturation, leukocytes > 11 × 10⁹/
µL, neutrophils > 7.5 × 10^3/µL, lymphocytes < 1 × 10^3/µL, and higher levels of creatinine, aspartate aminotransferase, lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer, among others (Table 4). Regarding the NP viral load, values over the second quartile and second tertile were also associated with unfavorable outcome in the unadjusted logistic regression analysis (Table 4).

In the final multivariable analysis, despite the previous link between a higher viral load and the occurrence of unfavorable outcome, the number of virus copies in the NP swabs was not independently associated with an unfavorable clinical result (Table 5). Five of the previous predictors were independently associated with increased odds of ICU admission and/or death: age ≥ 70 years (odds ratio [OR] 3.58, p < 0.001), SpO2 < 95% (OR 11.07, p < 0.001), neutrophils > 7.5 × 10^3/µL (OR 3.67, p = 0.001), LDH ≥ 300 U/L (OR 2.11, p = 0.04), and CRP ≥ 100 mg/L (OR 2.61, p = 0.01). Information on the overall apparent performance of the model is presented in Table 5 and Fig. 1.
Discussion
The main finding of the present study is that patients with SARS-CoV-2 infection, regardless of their illness severity, generally have a high rate of viral replication in the upper respiratory airways. Consequently, this parameter cannot be used as a predictor of COVID-19 unfavorable outcome, defined as admission to ICU and/or death. Moreover, this prospective cohort confirms that the independent risk factors for ICU admission or death are those previously identified by Salto-Alejandre S. et al. Thus, at first hospital evaluation, advanced age, hypoxemia, neutrophilia, and increased levels of LDH and CRP have high sensitivity and specificity to accurately discriminate patients that would potentially develop a critical disease from those with a favorable course.

The evidence to date reveals that the relationship between SARS-CoV-2 viral load and the pathogenicity and virulence of this microorganism is not fully understood. Furthermore, as there are many methods to perform the molecular detection of SARS-CoV-2 genome, the interpretation and comparison of results in literature is highly controversial. As an example, droplet digital PCR (ddPCR) has shown slightly higher sensitivity than standard RT-PCR.

### Table 5. Independent predictors of unfavorable outcome (ICU admission and/or death): Multivariable logistic regression model.

The final multivariable model was composed of five variables (therefore 17 events per variable) demonstrated as independent predictors of unfavorable outcome: Age ≥ 70 years, SpO2 < 95%, neutrophils > 7.5 × 10³/µL, LDH ≥ 300 U/L, and CRP ≥ 100 mg/L. Such model reported a Beta Coefficient of -4.08 (standard error = 0.46), a Wald statistic of 78.72 (degrees of freedom = 1), and an overall apparent performance of 84.2% (sensitivity = 70.6%, specificity = 89.4%, PPV = 70.3%, NPV = 89.1%). The variables included were explanatory and contributed to giving the model an ability to explain roughly 52.1% of the variation of the outcome (Nagelkerke R² value = 0.521). A higher nasopharyngeal viral load (above the second quartile or the second tertile) was not independently linked to an increased risk of ICU admission or death.

| Predictor                                      | Adjusted odds ratio (95% CI) | p value |
|------------------------------------------------|------------------------------|---------|
| Age ≥ 70 years                                  | 3.58 (1.83–6.99)             | <0.001  |
| SpO₂ < 95%                                      | 11.07 (5.34–22.97)           | <0.001  |
| Neutrophils > 7.5 × 10³/µL                      | 3.67 (1.74–7.74)             | 0.001   |
| LDH ≥ 300 U/L                                   | 2.11 (1.04–4.31)             | 0.04    |
| CRP ≥ 100 mg/L                                  | 2.61 (1.32–5.14)             | 0.01    |
| Viral load ≥ 7.35 log₁₀ copies/ml (50th percentile) | 1.49 (0.75–2.96)     | 0.25    |
| Viral load ≥ 8.27 log₁₀ copies/ml (2nd tertile)  | 1.84 (0.92–3.68)             | 0.09    |

### Figure 1. Discrimination power of the final multivariable model: ROC Curve plot.

Discrimination power of the model (including Age ≥ 70 years, SpO₂ < 95%, neutrophils > 7.5 × 10³/µL, LDH ≥ 300 U/L, and CRP ≥ 100 mg/L) expressed by an area under the ROC Curve of 0.89 (95% CI 0.85–0.93), standard error of 0.02 (under the non-parametric assumption), and p < 0.001 (being the null hypothesis a true area = 0.50).
Several previous studies have demonstrated that a high value of SARS-CoV-2 viral load in the upper respiratory tract (URT), defined as a Ct < 25 or < 22 in the RT-PCR, is an independent risk factor for respiratory failure, intubation, or death, using multivariate logistic regression and time-based analyses. Pujadas et al., using a Cox proportional hazards model, also showed an independent association between viral load in the URT and mortality.

Such results have often led to the thought that viral load could be used along with other features to decide upon the need for hospital admission, and even that a stratification for baseline NP viral load would benefit the design of clinical trials. Nevertheless, other studies show contradictory results. Maltezou et al., using a Ct < 25 to define high URT viral load, reported an association between higher viral load and the development of COVID-19 disease, while no association was found with ICU admission, mechanical ventilation or death. Amadio et al. demonstrated that the median PCR Ct was significantly lower in patients who died or needed critical care than in those who were hospitalized and discharged alive, or exclusively attended at home, but after adjusting for age and sex, there was not and independent association with critical care need or death.

Similarly, in our study, despite the patients with higher viral load (above the first tertile, the 50th percentile, and the second tertile) often belonged to the severe disease group, the adjusted multivariable model did not find an association between the copies per mL and the need for critical care or mortality. Argyropoulos et al., on the other hand, showed that viral load was inversely correlated with disease severity, being higher in patients with mild COVID-19. The reason for this conflicting result was, however, that NP sampling in patients with severe or critical symptoms was obtained at a later time point in the disease course. Lastly, Lee et al. found that viral load quantification was similar among symptomatic and asymptomatic patients, and our results support this conclusion. Certainly, most patients in the present cohort who suffered an unfavorable outcome had a high SARS-CoV-2 viral load quantification (above the 50th percentile) at hospital admission, but half of the patients with mild COVID-19 also exceeded said limit. This corroborates that the number of virus copies is not strongly related to COVID-19 prognosis.

To further test our hypothesis, we stratified the patients according to disease severity at the end of follow-up, and having confirmed that the medium time from symptoms onset to diagnosis was similar among groups, we performed multiple comparations for each viral load cut-off value. Mild patients could only be distinguished through the first tertile, above which a small increment of moderate and severe cases was found. For higher viral load cut-off points, the probability of belonging to the mild or moderate group was similar. The percentage of patients having NP viral load over the 50th percentile and second tertile was significantly higher for those with severe COVID-19, and the univariable analysis showed that a viral load quantification over the mentioned levels could be a risk factor for ICU admission or death. However, through the multivariable model, we concluded that a high viral load could not be used as an independent predictor of such outcomes.

Our study highlights several substantial issues. First, there is not a clear viral load cut-off point capable of discriminating between the various levels of COVID-19 severity, as the ROC Curve analysis demonstrated. Secondly and contrary to expectations, a higher number of SARS-CoV-2 copies in NP swabs at first patient's evaluation is not predictive of whether ICU admission or death might occur. Nevertheless, according to the Spanish nationwide seroepidemiological study, this finding should not be surprising: a third of the population with positive PCR was asymptomatic, and 20% of the seropositive symptomatic participants did not have previous SARS-CoV-2 genome detection. Finally, through the external cohort validation of hypoxemia, neutrophilia, and increased levels of LDH and CRP as independent predictors of unfavorable outcome, we contribute to the identification of high-risk patients with COVID-19 in whom treatment should be initiated.

The main strength of the present study is that a wide spectrum of COVID-19 severity, from mild symptomatic to critically ill patients, is represented in the analyzed cohort, allowing novel conclusions to be drawn about the efficacy and predictive reliability of previously studied clinical factors. The study has also some limitations. The viral load quantification in the URT samples, through NP swabs, was only performed at a single time point, and we have not data on the dynamics according to the clinical outcomes. Additional synchronous and longitudinal sampling from other sources, such as blood or stools, would have been important comparators. Regarding the quantification of SARS-CoV-2 viral load, further studies are required to refine the use of the standard and novel techniques, which is especially important due to variabilities in specimen collection, the lack of systematic quantification assays, and inconsistencies in protocols between different laboratories. Also, the lack of association of NP viral load with unfavorable outcome, should be confirmed when COVID-19 be caused by the new SARS-CoV-2 variants.

In summary, we found that higher values of SARS-CoV-2 viral load in NP samples at first hospital evaluation are more frequent in patients with unfavorable in-hospital outcome, but that a high viral load is not an independent risk factor for ICU admission or death among adult patients with COVID-19.

Methods
Design, patients, and data collection. We conducted a prospective observational cohort study in Virgen del Rocio University Hospital, a Spanish care-teaching center with 1177 beds (including 72 adult ICU beds). The study protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocio University Hospitals (C.I. 0771-N-20), and complied the Declaration of Helsinki. An informed consent was established as a mandatory requirement for all patients. Consecutive patients with confirmed COVID-19 by RT-PCR assay for SARS-CoV-2 in NP samples were enrolled, from February 29th to May 1st, 2020. Baseline was the date of first hospital evaluation. Follow-up censoring date was May 29th, 2020, for a minimum observation period in each patient of 28 days.
The clinical data source was the electronic medical record system. Variables registered included demographics, comorbidities, symptoms and signs at admission, baseline laboratory tests and chest X-ray findings, complications during hospitalization, and clinical outcome.

**SARS-CoV-2 infection diagnosis and viral load.** SARS-CoV-2 total RNA was extracted from NP swabs using EZ1 Virus Mini Kit v2.0 (Qiagen Inc., Valencia, CA, USA) following manufacturer’s instruction. SARS-CoV-2 genomic RNA was amplified by LightCycler 96 Instrument (Roche, Germany) using CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel and the GoTaq® Probe 1-Step RT-qPCR System (Wisconsin, USA) following the CDC’s instructions. The Quantitative Synthetic SARS-CoV-2 RNA: ORF E, N kit (ATCC, VA, USA) for each NP sample was run and Ct values were interpolated into the curve obtained to calculate the viral load in \( \log_{10} \) copies/mL. The lower and upper limits of quantification for our RT-PCR were 3.9 and 8.9 \( \log_{10} \) copies/mL, respectively.

**Statistical analysis.** Primary endpoint was the occurrence of unfavorable outcome at the end of follow-up, defined as a composite of ICU admission and/or death. For analyzing the ability of NP SARS-CoV-2 viral load at first patient’s evaluation to predict an unfavorable outcome, the severity of COVID-19 at the end of the 28 days follow-up was categorized into (1) mild, patients exclusively attended as outpatients after the first hospital evaluation; (2) moderate, hospitalized with full recovery and discharged; and (3) severe, hospitalized and admitted to the ICU or dead.

A descriptive analysis of all data obtained was performed. Categorical variables were presented as n (%) and continuous as median (interquartile range [IQR]). We used the \( \chi^2 \)-test, Fisher’s Exact Test, One-Way Analysis of Variance (ANOVA), Kruskal Wallis Test, Student’s \( t \)-test, or Welch’s \( t \)-test to compare between-group differences, and linear regression analysis to assess association between variables, as appropriate.

To examine the factors associated with unfavorable outcome, a univariable logistic regression analysis was performed. Additionally, bivariate correlations were thoroughly explored to account for potential confusion and interaction effects. To increase the applicability of our results within the scope of clinical practice, continuous variables were dichotomized based on normal ranges and cut-off values previously identified as predictors of unfavorable outcome.

Regarding SARS-CoV-2 viral load, for which there is no prior clinical consensus for categorization, we tried to determine the optimal cut-off value through a ROC curve plot (figure not shown). However, all the points in the curve approached the diagonal segment, with an area underneath of 0.57 (close to the null value) that called into question the usefulness of this parameter. Finally, we decided to analyze viral load based on three prespecified cut-off points: the first tertile, the second quartile or 50th percentile, and the second tertile.

For identifying which of the predictors obtained from the univariable analysis were to be considered independent, a multivariable logistic regression model was built using three criteria to achieve the highest accuracy: relevance to clinical situation, statistical significance (\( p < 0.10 \)), and adequate number of events to allow meaningful analysis. An automated backward stepwise selection was used for exclusion of variables, utilizing a probability threshold of 5%. The model was first assessed for sensitivity, specificity, positive and negative predictive values, and overall apparent performance. Secondly, the fraction of variance explained by said model was estimated through the Nagelkerke \( R^2 \) value. The internal validity was finally evaluated using the area under the ROC curve, where \( \geq 0.70 \) (being the null hypothesis a true area of 0.50) is considered as evidence of good discrimination ability.

**Ethics approval.** The study protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocio University Hospitals (C.I. 0771-N-20) and complied the Declaration of Helsinki.

**Data availability**
All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

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Author contributions
J.S.-C., E.C., J.M.C., and J.P. conceived and designed the study; obtained public funding from the Spanish Ministry of Economy, Industry, and Competitiveness; and took responsibility for the integrity of the data and the accuracy of its analysis. J.P., J.B.-C., and S.S.-A. did the scientific literature search. P.C.-M., C.I.-D., M.C.-L., J.C.C.-R., E.M., J.M.L., C.B., R.A., and J.A.L. provided the data. JB-C and SS-A processed the data, did the statistical analysis, and wrote the draft of the manuscript. All authors critically revised the manuscript for important intellectual content and gave final approval for the version published.

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Competing interests
The authors declare no competing interests.

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