Short communication

Survival in adult pneumonia inpatients fulfilling suspected COVID-19 criteria and baseline negative RT-qPCR

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ABSTRACT

Objectives: The objective of this study was to evaluate the survival experience of suspicion COVID-19 hospitalized patients with pneumonia and negative baseline reverse-transcription quantitative polymerase chain reaction (RT-qPCR) test results.
Study design: We conducted a nationwide retrospective cohort study in Mexico.
Methods: Adult pneumonia inpatients fulfilling suspected COVID-19 criteria, and hospital entry from March to August 2020, were enrolled. The Kaplan–Meier method was to use to compare survival estimates among patients with negative RT-qPCR nasopharyngeal or oropharyngeal swabs and those with a baseline positive test.
Results: Data from 64,624 individuals fulfilling suspected COVID-19 criteria were analyzed and 1.6% of them had negative RT-qPCR tests. The overall mortality rate was higher among laboratory-positive patients (48.5% vs. 34.2%, $P < 0.001$) and, at any given threshold, the survival estimates were higher among RT-qPCR–negative pneumonia inpatients.
Conclusions: The pathogenic mechanism of COVID-19 remains poorly understood and suspected cases with pneumonia and negative laboratory results represent a major challenge for healthcare systems. Our findings suggest that RT-qPCR–negative inpatients may have an improved disease prognosis, but the in-hospital mortality was still high among them. However, further research is needed to clarify the clinical and epidemiological implications of our results.

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The coronavirus disease 2019 (COVID-19) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic needs an opportune and accurate medical diagnosis to provide early management, patient allocation into healthcare settings, and to reduce the community viral spread.[1] Reverse-transcription quantitative polymerase chain reaction (RT-qPCR) is the gold standard for SARS-CoV-2 infection diagnosis; however, its sensitivity may be as low as 38%.[2]

The clinical management of suspicion COVID-19 cases with pneumonia and negative RT-qPCR may be challenging, particularly in settings with high viral transmission like Mexico where, by the start of November, more than 933,000 laboratory-confirmed cases and 92,000 deaths had been registered.[3]

To the best of our knowledge, there are not published studies evaluating the survival of pneumonia inpatients with clinical

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characteristics of COVID-19 but with negative analytical evidence. This study aimed to evaluate the survival experience of pneumonia inpatients with suspicion COVID-19 and negative baseline RT-qPCR test results.

We performed a retrospective and nationwide cohort study during October 2020 in Mexico. A broader description of the study methods was previously published.[4] Suspicions COVID-19 adult (aged 20 years or older) inpatients with clinical (SpO2 <94% on room air at sea level, a ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%)[5] and radiographical (polished glass, bilateral opacities, or consolidation areas in computed tomography scan)[6] findings of pneumonia, with illness onset from February to August 2020, were potentially eligible.

A total of 1066 adults with baseline negative upper respiratory (nasopharyngeal or oropharyngeal) swabs were identified and 53 of them were excluded due to missing data about the disease outcome; 3045 pneumonia patients by laboratory-positive SARS-CoV-2 (from 66,656 eligible subjects) were excluded for the same reason.

The SARS-CoV-2 detection analytical procedure was also described previously.[4] We analyzed the survival time of hospitalized pneumonia patients measured as the time elapsed from the date of hospital entry (starting event) to the date of in-hospital death (final event). The censored variable was defined as the patients who did not present the event (did not die) during the follow-up period and the date of hospital discharge was used to compute the time at risk. The 95% confidence interval (CI) were also computed. The log-rank test was used to compare the survival experience of RT-qPCR–negative and –positive subjects.

This study was approved by the Local Committee for Health Research (601) of the Mexican Institute of Social Security.

Data from 64,624 pneumonia inpatients with clinical suspicion COVID-19 were analyzed. Individuals with baseline laboratory-confirmed COVID-19 by SARS-COV-2 ($n = 63,611$) were compared with those with negative RT-qPCR test results ($n = 1013$) on nasopharyngeal swabs. The overall mortality rate was 48.5% and 34.2% ($P < 0.001$) among subjects with positive and negative baseline RT-qPCR, respectively.

The median (interquartile range) elapsed days from illness onset to specimen collection was shorter in cases reported as negative to SARS-COV-2 (4[2–6] vs. 5[3–7], $P < 0.001$). Individuals with negative RT-qPCR were more likely to be female (43.9% vs. 39.7%, $P = 0.006$) and to have personal history of chronic illnesses (chronic obstructive pulmonary disease, 11.9% vs. 4.0%, $P < 0.001$; type 2 diabetes mellitus, 40.0% vs. 33.6%, $P < 0.001$; arterial hypertension, 47.1% vs. 41.1%, $P < 0.001$; chronic kidney disease, 16.0% vs. 6.7%, $P < 0.001$) and immunosuppression (any cause except for type 2 diabetes mellitus or renal disease, 9.1% vs. 2.3%, $P < 0.001$). No significant differences were observed between study groups in terms of age.

Fig. 1 summarizes the computed survival rates and, at any given threshold, they were higher among RT-qPCR–negative cases ($P < 0.001$). Survival estimates (negative vs. positive RT-qPCR, 95% CI) were as following: day 3 (from hospital admission), 89.4% (87.3%–91.1%) vs. 87.1% (86.8%–87.3%); day 7, 79.6% (76.7%–82.2%) vs. 72.7% (72.3%–73.1%); day 15, 62.9% (58.8%–66.7%) vs. 49.3% (48.8%–49.7%); and 46.5% (41.2%-51-7%) vs. 29.0% (28.4%–29.6%) at one month from hospital entry.

We characterized the survival experience of a large set of RT-qPCR–negative hospitalized patients with pneumonia and suspicion COVID-19. Our results suggest that, even when about a third (34.2% vs. 48.5%, $P < 0.001$.) of them had a fatal outcome, their survival rates were higher than those observed in patients with a baseline laboratory-positive result. However, and given the current knowledge of SARS-CoV-2 infection, our results must be carefully considered because it is unclear if these subjects were correctly classified by the RT-qPCR test result.

Factors affecting the RT-qPCR sensitivity are numerous and include mutations in the primer and probe-target regions in the SARS-CoV-2 genome and viral load kinetics.[7] Published data
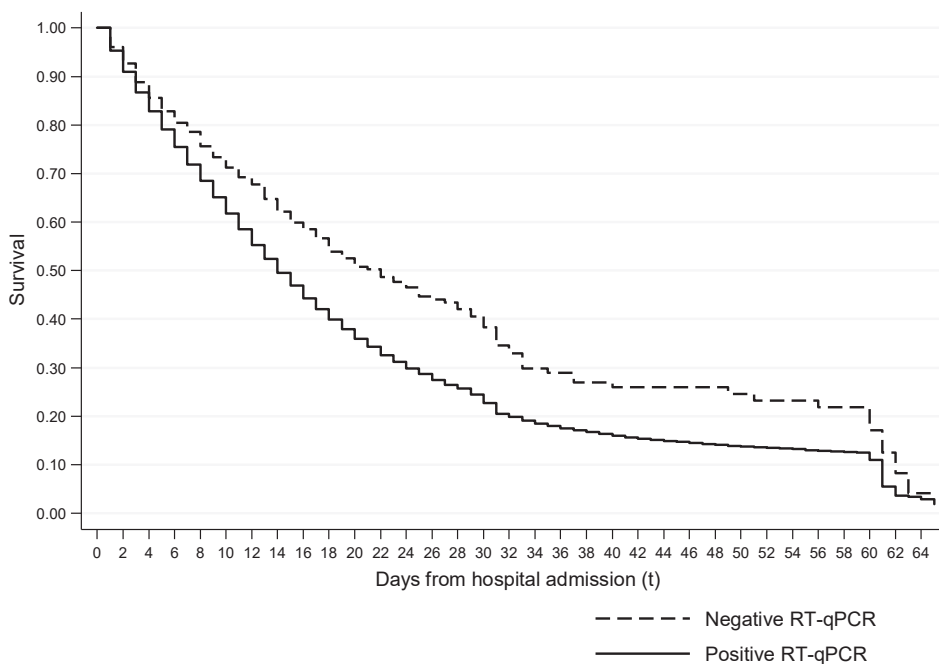

Fig. 1. Survival in adult pneumonia inpatients fulfilling suspected COVID-19 criteria with positive and negative baseline RT-qPCR test result, Mexico 2020. Abbreviations: **COVID-19**, coronavirus disease 2019; **RT-qPCR**, reverse-transcription quantitative polymerase chain reaction.

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suggest that increasing viral load is associated with the risk of COVID 19 mortality and may be determining, at least partially and given the high SARS-CoV-2 transmission rates documented in Mexico,[8] our findings.[9]

There are several potential limitations of our analysis. First, data regarding other respiratory viral pathogens were not available. This may be particularly relevant for the influenza virus; however, its transmission during the analyzed period (February to August 2020) is low. Second, the observed mortality in real-negative RT-qPCR pneumonia patients may be increased because pneumonic subjects are commonly allocated with other similar patients (despite the RT-qPCR result) and the nosocomial transmission of SARS-CoV-2 has been documented.[10]

The COVID-19 by SARS-CoV-2 remains poorly understood and, given the current analytical limitations in its diagnosis, the medical management of suspected cases with pneumonia and negative laboratory results represent a major challenge. Our findings suggest that baseline RT-qPCR—negative inpatients may have an improved disease prognosis but the in-hospital mortality was still high. However, further research is needed to clarify the clinical and epidemiological implications of our results.

Author statements

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Competing interests

None to declare.

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