Diagnostic performance and clinical implications of rapid SARS-CoV-2 antigen testing in Mexico using real-world nationwide COVID-19 registry data

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ABSTRACT (250 WORDS)

BACKGROUND: SARS-CoV-2 testing capacity is important to monitor epidemic dynamics. Given difficulties of large-scale RT-PCR implementation, rapid antigen tests (Rapid Ag-T) have been proposed as alternatives in settings such as Mexico.

OBJECTIVES: To evaluate diagnostic performance of Rapid Ag-T for SARS-CoV-2 infection and its associated clinical implications compared to RT-PCR testing in Mexico.

METHODS: We analyzed data from the COVID-19 registry of the Mexican General Directorate of Epidemiology up to December 31st, 2020 (n=3,374,165) and cases with both RT-PCR and Rapid Ag-T (n=18,446). We evaluated diagnostic performance using accuracy measures and assessed time-dependent changes in AUROC. We also explored test discordances as predictors of hospitalization, intubation, severe COVID-19 and mortality.

RESULTS: Rapid Ag-T is primarily used in Mexico City. Rapid Ag-T have low sensitivity 37.6% (95%CI 36.6-38.7), high specificity 95.4% (95%CI 95.1-95.8) and acceptable positive 86.1% (95%CI 85.0-86.6) and negative predictive values 67.2% (95%CI 66.2-69.2). Rapid Ag-T has optimal diagnostic performance up to days 7-10 after symptom, and its performance is modified by testing location, comorbidity, and age. RT-PCR(-) / Rapid Ag-T(+) cases had higher risk of adverse COVID-19 outcomes and were older, RT-PCR(+)/ Rapid Ag-T(-) cases had slightly higher risk or adverse outcomes and ≥7 days from symptom onset. Cases detected with rapid Ag-T were younger, without comorbidities, and milder COVID-19 course.

CONCLUSIONS: Rapid Ag-T could be used as an alternative to RT-PCR for large scale SARS-CoV-2 testing in Mexico. Interpretation of Rapid Ag-T results should be done with caution to minimize the risk associated with false negative results.

Keywords: SARS-CoV-2; rapid antigen testing; RT-PCR; Mexico; COVID-19

INTRODUCTION

SARS-CoV-2 testing capacity has been regarded as a fundamental factor to achieve pandemic control around the world[1]. It has been proposed that prompt isolation of possibly contagious individuals identified by testing and contact tracing is one of the most effective measures to reduce community-level transmission of SARS-CoV-2 infection; furthermore, effective reduction of community-level transmission can only be achieved with well-designed, universal, and cost-effective testing strategies[2]. Although reverse transcription polymerase chain reaction tests (RT-PCR) have been the reference for detection of active SARS-CoV-2 infections, its systematic implementation entails significant technical difficulties in limited resource settings[3]. In order to address these methodological issues, the World Health Organization (WHO) proposed that rapid antigen tests (Rapid Ag-T) and other point-of-care tests (POCTs), which have demonstrated to have a high specificity compared to other molecular techniques[4,5], could be useful alternatives for large-scale epidemiologic monitoring. With the worldwide rise in the use of Rapid Ag-T and POCTs, the presence of false negative results becomes of high epidemiologic importance, as unknown infected persons can be a vector of community transmission in countries where active SARS-CoV-2 infection is ongoing[8].

In Mexico, local authorities implemented a sentinel system-testing policy focused on tracking severe cases of COVID-19, and to a lesser extent those mild to moderate cases. Nevertheless, it has been reported that the implementation of full contact tracing procedure is only performed in areas where RT-PCR testing facilities are available[9]. Rapid Ag-T have been recently promoted as a dynamic strategy for detection of active SARS-CoV-2 infection in Mexico to address these issues; however, despite being recommended by the WHO and used worldwide, few studies have evaluated their performance using large epidemiological real-world data[6,7]. The increased use for Rapid Ag-T in Mexico demands a comprehensive evaluation for its diagnostic performance when compared to current reference testing techniques. Furthermore, its clinical implications could lead to the identification of subjects at risk for discrepancies of

Rapid Ag-T results to minimize the risk of complications from COVID-19 and streamline prompt medical care. Here, we aim to assess the performance of Rapid Ag-T for diagnosis of SARS-CoV-2 infection and to examine the clinical implications of the discrepancies in its result compared to RT-PCR test using national epidemiological dataset collected during the COVID-19 pandemic in Mexico.

METHODS

Data sources

This is a retrospective analysis of the open COVID-19 registry dataset collected by the General Directorate of Epidemiology of the Mexican Ministry of Health within the National Epidemiological Surveillance System (NESS), which includes daily updated suspected COVID-19 cases[10]. The database holds information on all persons tested for SARS-CoV-2 infection at public facilities in Mexico, as well as in all private healthcare facilities that follow the legal mandate to report COVID-19 cases to health authorities and the public locations for rapid antigen testing approved by the Mexican Ministry of Health. This report adheres to the STARD guidelines for reporting of diagnostic accuracy tests[11]. A full list of available variables is presented in **Supplementary Materials**.

Testing strategies for SARS-CoV-2 in Mexico

Prior to October 28th, 2020, suspected cases were tested for SARS-CoV-2 infection using real-time RT-PCR according to the Berlin Protocol[9]. Suspected COVID-19 cases were defined as an individual whom in the last 7 days has presented ≥2 of the following: cough, fever, or headache, accompanied by either dyspnea, arthralgias, myalgias, sore throat, rhinorrhea, conjunctivitis, or chest pain. Amongst suspected cases, the Ministry of Health established two protocols for case confirmation: 1) SARS-CoV-2 testing is done widespread for suspected COVID-19 cases with severe acute respiratory infection and signs of breathing difficulty or deaths with suspected COVID-19, 2) for all other cases, a sentinel surveillance model is being utilized, whereby 475 health facilities which comprise a nationally representative sample evaluate ~10% of mild outpatient cases to provide estimates of confirmed mild cases[9,12].

After October 28th, 2020, tests for SARS-CoV-2 infections additionally included those who were detected using one of the three available Rapid Ag-T including STANDARD™Q COVID-19 Ag Test, Panbio™ COVID-19 Ag RAPID Test Device, and Sofia2 SARS Antigen FIA by Quidel Corporation, which are approved by use and evaluated for efficacy by the National Institute for Epidemiological Diagnosis and Reference and the WHO[13]. These Rapid Ag-T are available in healthcare community-level locations for testing access of suspected COVID-19 cases or by epidemiological association with a suspected case and currently used for tracking the epidemic in Mexico City[14]. Confirmed SARS-CoV-2 infection is defined as an individual with a positive Rapid Ag-T or a positive RT-PCR test; all negative Rapid Ag-T with suspected epidemiological association with a confirmed SARS-CoV-2 case or a clinical profile with high suspicion of COVID-19 are eligible for further evaluation with RT-PCR testing within testing facilities[9].

Definitions of outcomes and predictors

For cases who had both RT-PCR and rapid antigen test information available, we used the RT-PCR result as a reference test to classify cases as true positive (RT-PCR + / Rapid Ag-T +), true negative (RT-PCR - / Rapid Ag-T -), false positive (RT-PCR - / Rapid Ag-T +) and false negative (RT-PCR + / Rapid Ag-T -). Severe outcomes were defined as a composite of either death, ICU admission or requirement for invasive ventilation; hospital admission, requirement for invasive intubation and lethality were also evaluated as outcomes. Follow-up time was estimated in days from symptom onset until either hospitalization or death, depending on the outcome of interest, or censoring up to last known follow-up, whichever occurred first.

Statistical analysis

Population-based statistics

We compared testing rates standardized per 100,000 inhabitants across Mexican municipalities and its trends over time after its implementation in late October comparing testing rates between Mexico City and the rest of Mexico due to the high density of Rapid Ag-T in the first. We also compared incident cases detected with RT-PCR and Rapid Ag-T in Mexico City compared to the rest of the country. Furthermore, we compared cases who were assessed exclusively with Rapid Ag-T, RT-PCR, or both to identify factors which influence testing in these settings.

Performance of rapid antigen tests compared to RT-PCR

We evaluated the performance of Rapid Ag-T compared to RT-PCR using complete-case analysis of individuals who had both results available using confusion matrices and areas under the receiving operating characteristic curves (AUROC) with the *caret* and *pROC* R packages. We further estimated sensitivity, specificity, positive and negative predictive values (PPV, NPV, respectively) and positive and negative likelihood ratios (LR+ and LR-, respectively) and its corresponding 95% confidence intervals with DeLong's method with the *OptimalCutpoints* R package. To evaluate the performance of Rapid Ag-T in different settings, we stratified these metrics according to testing location (Mexico City vs. Rest of Mexico), patient status (inpatient vs. outpatient), cases with and without comorbidities, age (>60 vs. ≤60 years) and time from symptom onset to evaluation (>7 vs ≤7 days from onset).

Time-dependent performance of rapid antigen tests

We evaluated time-varying diagnostic performance or Rapid Ag-T using time-dependent ROC curves with the *timeROC* R package with inverse probability weighting in Cox regression, adjusted for age and sex for 1, 3, 5, 7, 10 and 15 days from symptom onset. We further evaluated the performance of Rapid Ag-T to predict hospitalization, mortality, and intubation, in cases with or without added RT-PCR testing using the same proposed cut-offs.

Predictors of test discordances

We tested for predictors of Rapid Ag-T and RT-PCR discrepancies using mixed effects logistic regression, considering heterogeneity in epidemic dynamics across Mexico including municipality of residence as a random effect. To dissect predictors of test discrepancy, for false positive models we included only false positive and true negative cases and for false negative models we included true positive and false negative cases. We adjusted all models for age, sex, time from symptom onset and comorbidities.

Clinical implications of Rapid Ag-T

First, we evaluated predictors for hospitalization, lethality and the composite event of severe outcomes using time-to-event models under the proportional risk assumption with mixed-effects Cox regression incorporating municipality of residence as a random effect within the frailty term to control for geographical heterogeneity. Next, we evaluated the risk associated with true or false positives and false negatives in Rapid Ag-T compared to true negatives using RT-PCR for hospitalization, lethality and severe outcomes using mixed effects Cox regression models, adjusted for covariates. Both for outcome predictors and for the implication of test discordances on intubation rates, we fitted mixed effects logistic regression models adjusted for covariates and considering municipality of residence as a random effect. For Cox models, proportional risk assumptions were verified using Schönfeld residuals and visual inspection of time-varying effects; for logistic regression models, goodness of fit was evaluated using the Hosmer-Lemeshow test and model selection was carried out using minimization of the Bayesian Information Criterion (BIC). All statistical analyses were conducted using R language version 4.0.3 and a p-value <0.05 was considered as the statistical significance threshold.

RESULTS

Study population

Until December 31st, 2020 a total of 3,374,165 subjects had been tested for SARS-CoV-2 in Mexico. Amongst them, 3,009,578 had only an RT-PCR test, 340,484 had only a rapid antigen test and 24,103 subjects had both RT-PCR and rapid antigen tests. When comparing characteristics amongst the three previous groups, cases tested using Rapid Ag-T were younger, predominantly female, had lower rates of chronic comorbidities, and fewer cases who presented with features of severe COVID-19 including pneumonia, requirement for ICU admission, intubation, or death. Notably, cases who undertook Rapid Ag-T had lower median days from symptom onset to clinical assessment (**Table 1**).

Amongst tested cases, a total of 1,369,368 (40.6%) cases had confirmed SARS-CoV-2 infection using either of those tests and 2,004,797 (59.4%) had a negative result. The rate of positivity was lower for Rapid Ag-T compared to RT-PCR. After the implementation of Rapid Ag-T, the rate of testing using this method was the largest in Mexico City, with over 3,849.55 tests per 100,000 habitants, marginally followed by the state of Tabasco with 181.71 Rapid Ag-T per 100,000 habitants. As of December 31st, 2020, ~80% of SARS-CoV-2 testing in Mexico City is being carried out using Rapid Ag-T compared with <10% in the rest of Mexico. Overall, amongst 94,029 confirmed SARS-CoV-2 cases using Rapid Ag-T, 74,178 (78.9%) were confirmed in Mexico City (**Figure 1**). A STARD diagram depicting all evaluated cases and a histogram of time from onset to testing is presented in **Supplementary Material**.

Performance of rapid antigen tests compared to RT-PCR

A total of 24,103 subjects were tested using both RT-PCR and Rapid Ag-T. Amongst them, 3588 had pending tests results and 2069 had inadequate RT-PCR samples. Overall, a total of 18,446 cases had valid RT-PCR and rapid antigen test results (**Supplementary Materials**). These cases had higher rates of chronic comorbidities and COVID-19 complications compared to cases with Rapid Ag-T only, but lower rates compared to RT-PCR only (**Table 1**). Overall, we observed low concordance between both test modalities (κ=0.356, 95%CI 0.344-0.369); when considering RT-PCR as reference test, we identified 2968 true positives, 4917 false negatives, 479 false positives and 10,082 true negatives, yielding and AUROC of 0.666 (95%CI 0.660-0.671). Overall, we identified that rapid antigen tests have a sensitivity of 37.6% (95%CI 36.6-38.7) and a specificity of 95.4% (95%CI 95.1-95.8), with a PPV of 86.1% (95%CI 85.0-86.6), a NPV of 67.2% (95%CI 66.2-69.2), a LR+ of 8.3 (95%CI 7.6-9.1), and a LR- of 0.65 (95%CI 0.64-0.66). Next, we assessed how the Rapid Ag-T performed in different scenarios and identified a lower performance in Mexico City compared to the rest of Mexico, for outpatients, younger cases without comorbidities and, notably, in cases who had ≥7 days from symptom onset at evaluation.

Time-dependent variation in Rapid Ag-T performance

Given the aforementioned observation of time-varying performance according to the time from symptom onset, we used time-dependent ROC curves to model changes in diagnostic performance over time for detection of SARS-CoV-2 infection. We observed that, compared to RT-PCR, Rapid Ag-T had the better AUROC at 7 days and its performance subsequently decreased until reaching the lowest AUROC at 15 days after symptom onset, adjusted for age and sex. Next, we evaluated whether using one test modality provided better predictive capacity for hospitalization, intubation and mortality, which would have relevant clinical implications for test selection. We observed that a positive RT-PCR was best at predicting hospital admission between 7-10 days after symptom onset and mortality at days 10-15, without significant utility for intubation. For Rapid Ag-T, we observed similar trends, with an optimal window for mortality between days 7-10 after symptom onset (**Table 3**).

Clinical characterization of cases with discordant Rapid Ag-T results

We evaluated predictors of false positive and negative results in Rapid Ag-T for SARS-CoV-2 using RT-PCR as reference test. Cases with false negative results had ≥7 days from symptom onset, were younger, and predominantly female. Regarding comorbidities, cases with false negative results were less likely to have underlying immunosuppression, obesity and chronic kidney disease. Regarding false positive results, we only observed increasing age as a significant predictor, with a non-significant trend in cases with chronic kidney disease (**Figure 2**). Next, we investigated whether these test discordances were predictive of COVID-19 outcomes. Regarding hospitalization we observed that, compared to true negative results, risk for hospitalization was higher for cases with false positive (HR 1.79, 95%CI 1.43-2.24), false negative (HR 1.16, 95%CI 1.04-1.29) and true positive (HR 1.89, 95%CI 1.69-2.12) Rapid Ag-T results, adjusted for treatment setting, comorbidities, sex and age. Compared to true negative results, risk of intubation requirement was higher for false positive test results (OR 2.29, 95%CI 1.17-4.49) and lower for false negative results (OR 0.47, 95%CI 0.28-4.49). When assessing the composite of any severe outcome, we observed a higher risk for cases with false (HR 3.06, 95%CI 2.07-4.52), true positive results (HR 3.16, 95%CI 2.54-3.93) and for false negatives (HR 1.27, 95%CI 1.00-1.60). Finally, mortality risk was the highest for cases with true positive results (HR 4.41, 95%CI 3.39-5.74), followed by cases with false positive (HR 2.85, 95%CI 1.74-4.68) and false negative results (HR 1.86, 95%CI 1.41-2.46, **Figure 3**).

Characterization of SARS-CoV-2 positive cases using Rapid Ag-T

Finally, we compared positive cases detected using RT-PCR and Rapid Ag-T. As expected, positive SARS-CoV-2 cases detected using Rapid Ag-T have a wider spectrum of disease severity with correspondingly lower rates of hospitalization, intubation, mortality and pneumonia. Cases detected using Rapid Ag-T are younger with lower rates of comorbidity and, notably, less median days from symptom onset to evaluation. Amongst cases assessed using Rapid Ag-T, positive SARS-CoV-2 cases had higher risk for hospitalization in older adults, males and subjects with obesity, immunosuppression, CKD, COPD, diabetes o hypertension. For severe COVID-19 and mortality, we identified higher risk in those with CKD, immunosuppression, COPD, hypertension, diabetes, males and older adults (**Supplementary Material**).

DISCUSSION

Here, we performed a real-life large-scale evaluation of Rapid Ag-T for the detection of SARS-CoV-2 at a community-wide level in Mexico. Rapid Ag-T are primarily used in Mexico City for rapid detection of cases to promote self-isolation and prompt initiation of treatment in severe COVID-19 cases. Given the larger availability of Rapid Ag-T, tested cases are younger and have lower rates of comorbidities previously linked to high risk of severe COVID-19, thus leading to lower rates of severe outcomes likely reflective of the true spectrum of SARS-CoV-2 infection in the community[12,15]. We observed that age, comorbidity and time from symptom onset significantly impact the performance of Rapid Ag-T for SARS-CoV-2 and that optimal performance for these tests decreases after 7-10 days from symptom onset. Furthermore, we identified that positive Rapid Ag-T in cases with negative RT-PCR have higher risks for severe COVID-19 outcomes, indicating potential benefit for the use of Rapid Ag-T in addition to RT-PCR testing; notably, cases with false negative results in Rapid Ag-T have slightly higher risk of severe COVID-19 outcomes, with the main determinant for false negative status being the time from symptom onset to test assessment. Finally, older patients with negative RT-PCR had higher odds of a positive Rapid Ag-T, which might call for implementation of sequential testing using Rapid Ag-T after a negative RT-PCR in older adults with high clinical suspicion. Our results represent the largest evaluation on the usefulness of Rapid Ag-T in a real-world setting as well as on how some common chronic conditions might modify its accuracy in comparison with RT-PCR tests. With the recent but limited availability of vaccines to prevent symptomatic SARS-CoV-2, consistent prevention of community-level transmission remains paramount to reduce contagions and prevent mortality until an ideal vaccination threshold can be achieved[16]. In this setting, widespread, frequent and repeated use of Rapid Ag-T is preferable given the limited implementation of large-scale RT-PCR testing for SARS-CoV-2 in Mexico[4,17].

The use of POCTs is relevant in pandemic settings, where test results can be used to promote self-isolation, adequate treatment allocation and to further contact tracing to reduce rapid dissemination of SARS-CoV-2[18]. A recent meta-analysis of rapid POCTs for SARS-CoV-2 infection evaluated the use of Rapid Ag-T in different settings, identifying varying values of sensitivity coupled with high specificity, accordingly with our study[19]. The authors concluded that Rapid Ag-T can be used as a triage to allocate RT-PCR testing in limited resource settings, which is compatible with our assessment of the clinical implications of false negatives using Rapid Ag-T to detect SARS-CoV-2 infection[20]. Our results show that Rapid Ag-T yield a low sensitivity but a very high specificity for detection of SARS-CoV-2 when compared to RT-PCR. Despite the low sensitivity, the positive and negative predictive values are high likely due to the high prevalence of SARS-CoV-2 in the community[19]. This is consistent with reports of a re-analysis of published data of diagnostic accuracy of RT-PCR SARS-CoV-2 testing, which described that the risk of false positives increases when extending testing strategies, with increased in false negatives being attributable to local outbreaks[21]. In our study, Rapid Ag-T in Mexico City had a higher LR+ compared with the rest of the country, with equally high rates of false negative results using rapid antigen testing; notably, this testing modality is being used in this location to track trends of the COVID-19 pandemic. Special caution should be taken when evaluating and communicating negative results of rapid antigen tests for SARS-CoV-2, which if misinterpreted could be misleading and reduce adherence for self-isolation of asymptomatic cases identified via contact tracing[22].

Prior to the instauration of widespread Rapid Ag-T, the Mexican Ministry of Health selected cases for RT-PCR testing based on a sentinel-surveillance system which identified cases based on the presence of respiratory symptoms, leading to an overrepresentation of severe and critical COVID-19 cases[9]. Our group previously profiled cases with non-respiratory symptoms and asymptomatic SARS-CoV-2 infections in Mexico City; we identified that no single symptom offered a reliable assessment of disease severity at the time of initial evaluation, even in population at high risk of contagion such as healthcare workers, as has been confirmed by a recent meta-analysis[23–25]. Given recent evidence which highlights the potential of pre-symptomatic and asymptomatic SARS-CoV-2 transmission and the usefulness of contact tracing as a complement to social distancing and community mitigation policies, SARS-CoV-2 testing should be extended to cases with recent contact with known COVID-19 cases despite the absence of symptoms[22,26,27]. Unfortunately, POCTs have relevant limitations on its diagnostic performance which may question its widespread use to inform public policy or for clinical decision making. Particularly, Rapid Ag-T require an active and symptomatic infection and sampling must be done no later than 7 days after beginning of symptoms, while RT-PCR can be used to assess asymptomatic cases and requires less amount of sample to yield a positive result[28]. Our data similarly suggests that the time-varying diagnostic performance or Rapid Ag-T might have similar shortcomings to those observed in RT-PCR testing and which need to be considered when using the result of either method to inform decision-making[29,30]. Future studies should investigate the utility of Rapid Ag-T as triage for RT-PCR use in asymptomatic SARS-CoV-2 infection as well as the ideal time frames to reduce the likelihood of discordant results when implementing sequential testing.

Our study had some strengths and limitations. We are using a large national registry of COVID-19 cases, many of whom were tested using both Rapid Ag-T and RT-PCR in a real-world setting which allowed us to reasonably assess diagnostic performance of Rapid Ag-T to detect SARS-CoV-2 infection. We were also able to assess the clinical impact of discordant results on COVID-19 outcomes as well as predictors which indicate settings where additional testing might be useful to reduce the externalities associated with false negative results. Regarding the limitations to be acknowledged is the potential influence of a spectrum effect, where diagnostic accuracy measures vary according to COVID-19 prevalence and the potential detection bias of only testing most cases once, likely missing infections who were initially categorized as false negative with RT-PCR early in the course of infection[31,32]. Furthermore, the use of the sentinel surveillance system to detect and report COVID-19 cases in Mexico likely skews detection towards more severe cases who may also have longer time from symptom onset to evaluation, increasing time-dependent heterogeneity within estimation of predictive accuracy measures[29]. Finally, the lack of disaggregated symptom data prevents assessment of the influence of various symptom clusters in modifying disease detection with different testing modalities, which remains as an area of opportunity for future research[33].

In conclusion, Rapid Ag-T could be a useful strategy to extend SARS-CoV-2 screening and track trends of the COVID-19 pandemic in Mexico. Rapid Ag-T have poor sensitivity with high specificity but in a setting of local outbreaks, these tests might have high predictive values and be a helpful complement to contact tracing if properly implemented. Rapid Ag-T should be performed widely and frequently to increase the usefulness of low-sensitive tests and increase diagnostic accuracy as well as to guide allocation of RT-PCR testing in low-resource settings[4,19,34]. Our results could inform situations when a discordant result of Rapid Ag-T for SARS-CoV-2 could be expected and the associated clinical implication of using test results for policy and clinical decision making. The use of Rapid Ag-T warrants future evaluations regarding the influence of symptom presentation, recent contact with confirmed COVID-19 case and disease severity on test accuracy and its role in detecting asymptomatic infection as a complement to contact tracing.

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DATA AVAILABILITY

All data sources and R code are available for reproducibility of results at https://github.com/oyaxbell/covid_antigen_mx.

AUTHOR CONTRIBUTIONS

Research idea and study design OYBC, NEAV, LFC, ECG, AVV, JPBL, CAFM, AMS; data acquisition: OYBC, NEAV; data analysis/interpretation: OYBC, NEAV, LFC, ECG, AVV, CAFM, AMS, JPBL; statistical analysis: OYBC, NEAV; manuscript drafting: OYBC, NEAV, LFC, ECG, AVV, JPBL, CAFM, AMS; supervision or mentorship: OYBC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions about the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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TABLES

Table 1. Characteristics of subjects tested for SARS-CoV-2 infection in Mexico, comparing cases who were tested using RT-PCR, rapid antigen tests and a combination of both.

Abbreviations: RT-PCR: Reverse transcription polymerase chain reaction; CKD, Chronic Kidney Disease; CVD: cardiovascular disease; COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; 95%CI: 95% Confidence interval, ICU: Intensive Care Unit.

Parameters	RT-PCR test n=3009578	Rapid antigen test n=340484	Both tests n=24103	p-value
Age (years)	41.6±17	38.6±16.1	40.8±16.5	<0.001
Male sex (%)	1,453,173 (48.3)	159,819 (46.9)	11,024 (45.7)	<0.001
Confirmed SARS-CoV-2 (%)	1,275,339 (42.4)	84,608 (24.8)	9,421 (39.1)	<0.001
Diabetes (%)	346,166 (11.5)	22,507 (6.6)	2,446 (10.1)	<0.001
COPD (%)	35,236 (1.2)	1,180 (0.3)	165 (0.7)	<0.001
Asthma (%)	81,530 (2.7)	6,578 (1.9)	619 (2.6)	<0.001
Immunosuppression (%)	32,354 (1.1)	1,289 (0.4)	188 (0.8)	<0.001
Hypertension (%)	465,640 (15.5)	31,064 (9.1)	3,226 (13.4)	<0.001
Other (%)	66,550 (2.2)	518 (0.2)	295 (1.2)	<0.001
CVD (%)	51,871 (1.7)	2,458 (0.7)	324 (1.3)	<0.001
Obesity	422,000 (14)	24,962 (7.3)	2,723 (11.3)	<0.001
CKD (%)	48,518 (1.6)	1,323 (0.4)	274 (1.1)	<0.001
Smoking (%)	247,446 (8.2)	35,328 (10.4)	2,536 (10.5)	<0.001

Parameters	RT-PCR test n=3009578	Rapid antigen test n=340484	Both tests n=24103	p-value
Pneumonia (%)	323,413 (10.7)	2,766 (0.8)	2,434 (10.1)	<0.001
Hospitalization (%)	461,022 (15.3)	1,798 (0.5)	3,110 (12.9)	<0.001
ICU admission (%)	417,292 (13.9)	1,746 (0.5)	2,981 (12.4)	<0.001
Death (%)	158,148 (5.3)	341 (0.1)	616 (2.6)	<0.001
Time to assessment* (days)	3 (1-5)	2 (0-4)	3 (1-5)	<0.001

Table 2. Overall diagnostic performance metrics of rapid antigen tests to detect SARS-CoV-2 infection compared to RT-PCR in Mexico and stratification by region of testing, patient setting, comorbidity, age and days from symptom onset to evaluation.

Abbreviations: FP: False positive; FN: False negative; PPV: Positive Predictive Value; NPV: Negative Predictive Value, LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio, RT-PCR: Reverse transcription polymerase chain reaction; AUROC: Area under the receiving operating characteristic curve.

Parameter	FP/FN	AUROC (95%CI)	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	PPV (%, 95%CI)	NPV (%, 95%CI)	LR+ (95%CI)	LR- (95%CI)
Overall	479./4917	0.666 (0.66-0.671)	37.6 (36.6-38.7)	95.5 (95.1-95.9)	86.1 (85-86.6)	67.2 (66.2-69.2)	8.3 (7.6-9.1)	0.65 (0.64-0.66)
Mexico City	255/4108	0.658 (0.652-0.664)	34.5 (33.3-35.6)	97.1 (96.8-97.5)	89.4 (88.2-89.9)	67.8 (66.6-70.5)	12.0 (10.6-13.6)	0.67 (0.66-0.69)
Rest of Mexico	224/809	0.683 (0.668-0.698)	50.0 (47.5-52.5)	86.6 (84.9-88.2)	78.3 (75.8-79.9)	64.2 (61.9-67.5)	3.7 (3.3-4.3)	0.58 (0.55-0.61)
Outpatient	370/4195	0.652 (0.646-0.658)	34.2 (33.1-35.4)	96.2 (95.8-96.6)	85.5 (84.2-86.2)	69.1 (68-71.4)	9.0 (8.1-10.0)	0.68 (0.67-0.70)
Inpatient	109/722	0.692 (0.674-0.709)	52.0 (49.5-54.6)	86.3 (83.8-88.6)	87.8 (85.4-88.8)	48.8 (46.3-54.1)	3.8 (3.2-4.6)	0.56 (0.52-0.59)
No comorbidities	294/3092	0.660 (0.653-0.667)	36.3 (35-37.7)	95.7 (95.2-96.2)	85.7 (84.2-86.4)	67.8 (66.5-70.4)	8.4 (7.5-9.5)	0.67 (0.65-0.68)
≥1 comorbidity	182/1811	0.674 (0.665-0.684)	39.7 (38-41.5)	95.1 (94.4-95.8)	86.8 (85-87.6)	66.1 (64.5-69.5)	8.1 (7.0-9.4)	0.63 (0.61-0.65)

Parameter	FP/FN	AUROC (95%CI)	Sensitivity (%, 95%CI)	Specificity (%, 95%CI)	PPV (%, 95%CI)	NPV (%, 95%CI)	LR+ (95%CI)	LR- (95%CI)
<60 years	392/4164	0.657 (0.651-0.663)	35.6 (34.4-36.8)	95.8 (95.4-96.2)	85.4 (84.1-86.1)	68.3 (67.2-70.5)	8.5 (7.7-9.4)	0.67 (0.66-0.69)
≥60 years	87/753	0.699 (0.684-0.714)	47.0 (44.4-49.7)	92.7 (91.1-94.1)	88.5 (86.1-89.5)	59.6 (57-65)	6.5 (5.2-8)	0.57 (0.54-0.6)
<7d from onset	432/4050	0.674 (0.668-0.68)	39.3 (38.1-40.5)	95.5 (95.1-95.9)	85.8 (84.6-86.4)	69.5 (68.4-71.5)	8.8 (8-9.7)	0.64 (0.62-0.65)
≥7d from onset	47/867	0.618 (0.603-0.632)	28.6 (26.1-31.3)	94.9 (93.2-96.2)	88.1 (84.7-89.4)	50.1 (46.9-57.9)	5.6 (4.2-7.5)	0.75 (0.72-0.78)

Table 3. Time-dependent area under ROC curves using inverse weighted probability with Cox regression for detection of SARS-CoV-2 infection, adjusted for age assessing the performance of rapid antigen tests compared to RT-PCR at days 1, 3, 7, 10 and 15. The table also shows the ability of RT-PCR or rapid antigen tests to predict hospitalization, intubation and mortality related to COVID-19 at these different time points.

Abbreviations: AUROC: Area under the receiving operating characteristic curve; RT-PCR: Reverse transcription polymerase chain reaction; Ag-T: Rapid Antigen test.

Time AUROC	RT-PCR vs. Ag-T	RT-PCR Hospitalization	Ag-T Hospitalization	RT-PCR Intubation	Ag-T Intubation	RT-PCR Mortality	Ag-T Mortality
1 day	0.548	0.476	0.546	0.258	0.341	0.570	0.628
3 days	0.598	0.520	0.542	0.330	0.41	0.640	0.619
7 days	0.609	0.592	0.612	0.391	0.547	0.673	0.691
10 days	0.593	0.648	0.593	0.489	0.600	0.736	0.694
15 days	0.523	0.581	0.523	0.65	0.503	0.709	0.417

FIGURE LEGENDS

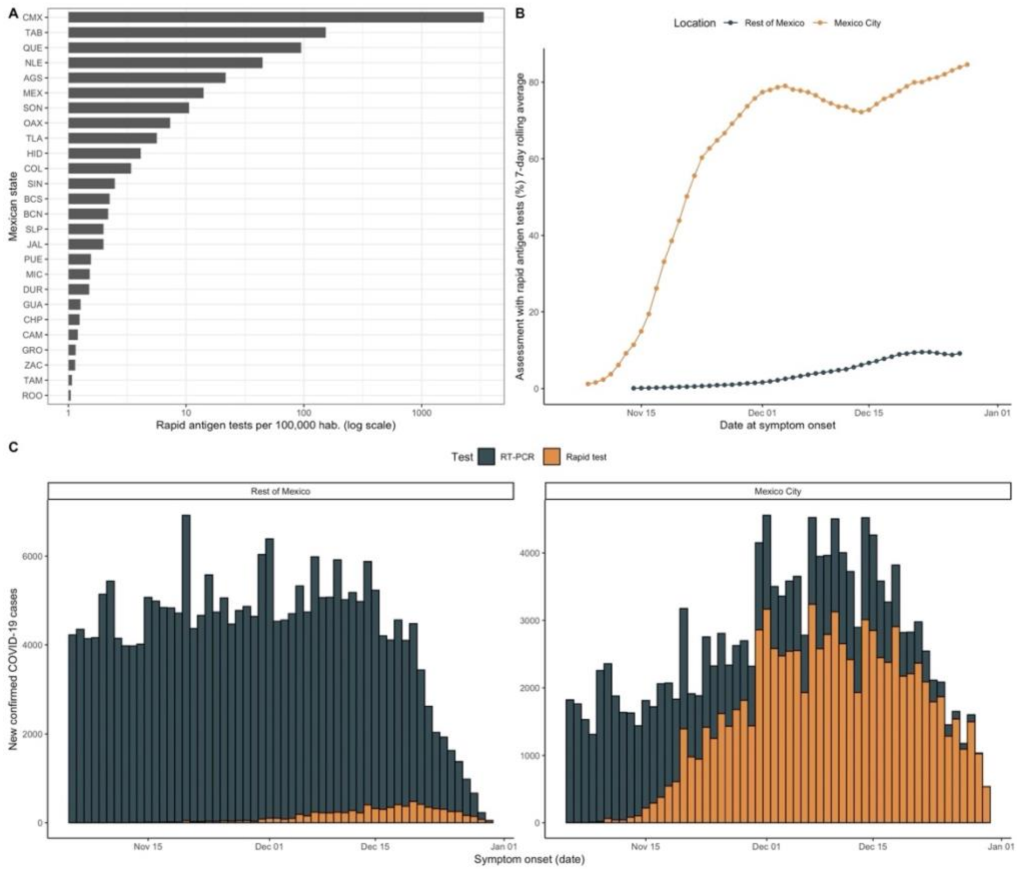


Figure 1. A) Number of rapid antigen tests per 100,000 population across different Mexican states. Figure also shows the percentage of rapid antigen tests amongst all SARS-CoV-2 tests administered in Mexico City and the rest of Mexico (B) and the curve of confirmed cases according to date from symptom onset in Mexico City and the rest of Mexico (C-D).

<u>Abbreviations:</u> RT-PCR: Reverse transcription polymerase chain reaction

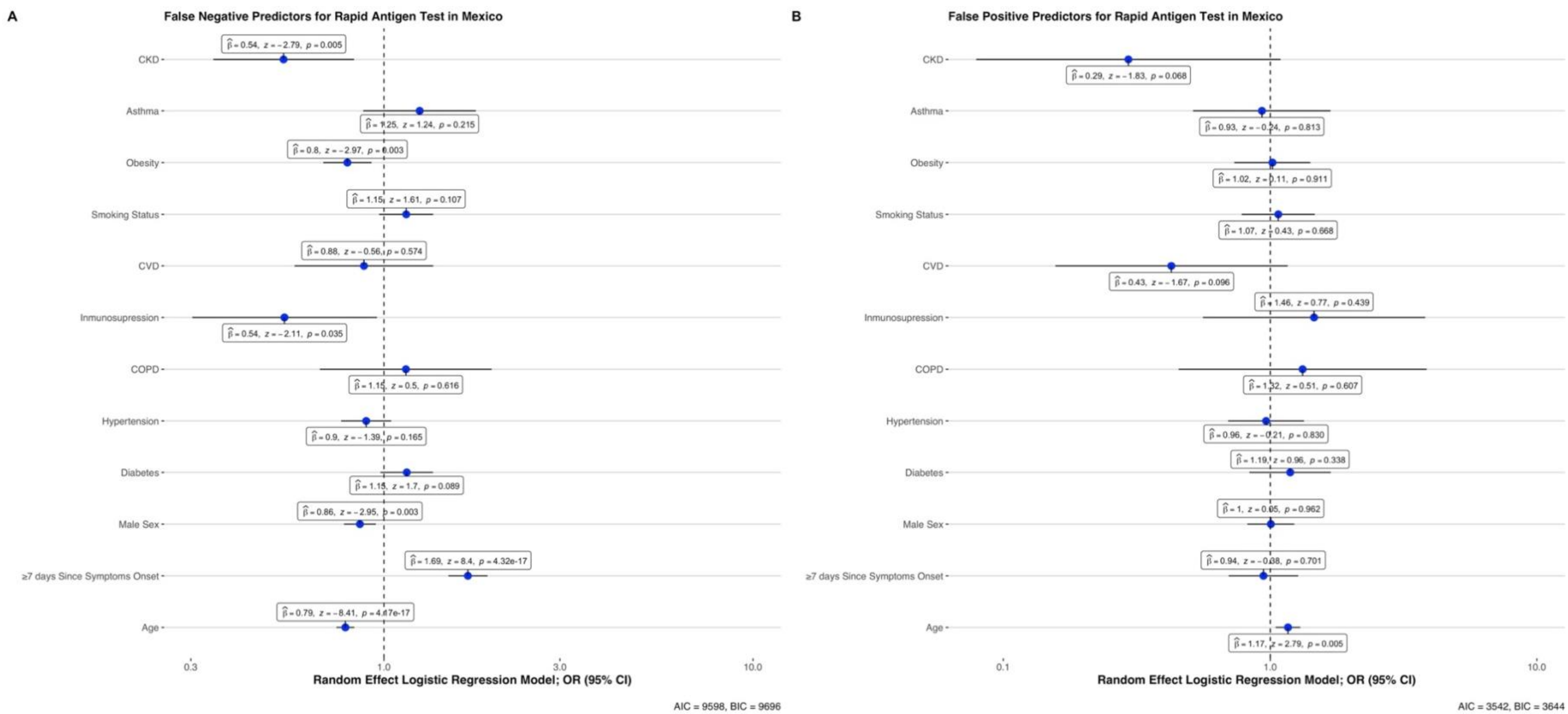


Figure 2. Mixed effects logistic regression models assessing predictors of cases with false negative compared to true positive test results (A) and false positive compared to true negative test results (B) using RT-PCR as reference tests.

Abbreviations: RT-PCR: Reverse transcription polymerase chain reaction; CKD, Chronic Kidney Disease; CVD: cardiovascular disease; COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; 95%CI: 95% Confidence interval, ICU: Intensive Care Unit

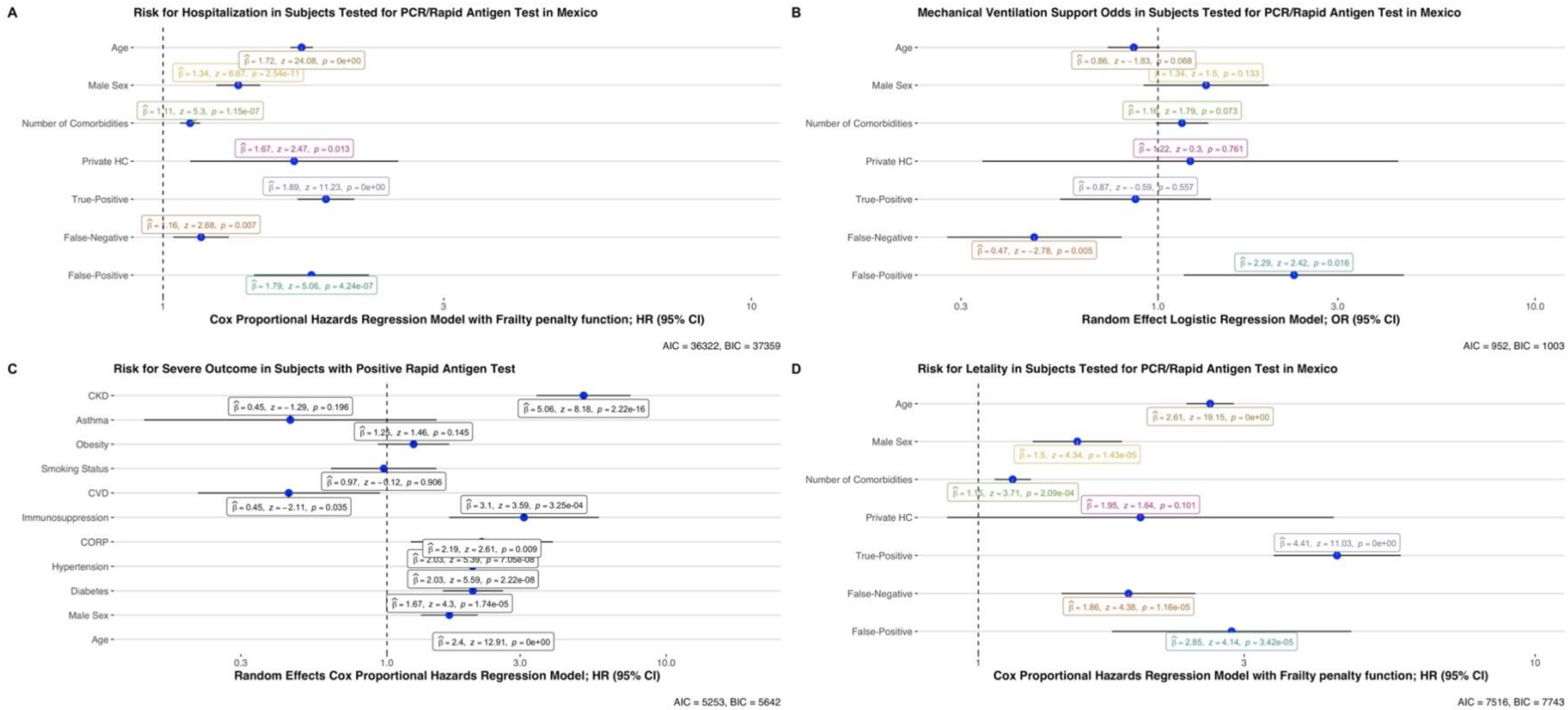
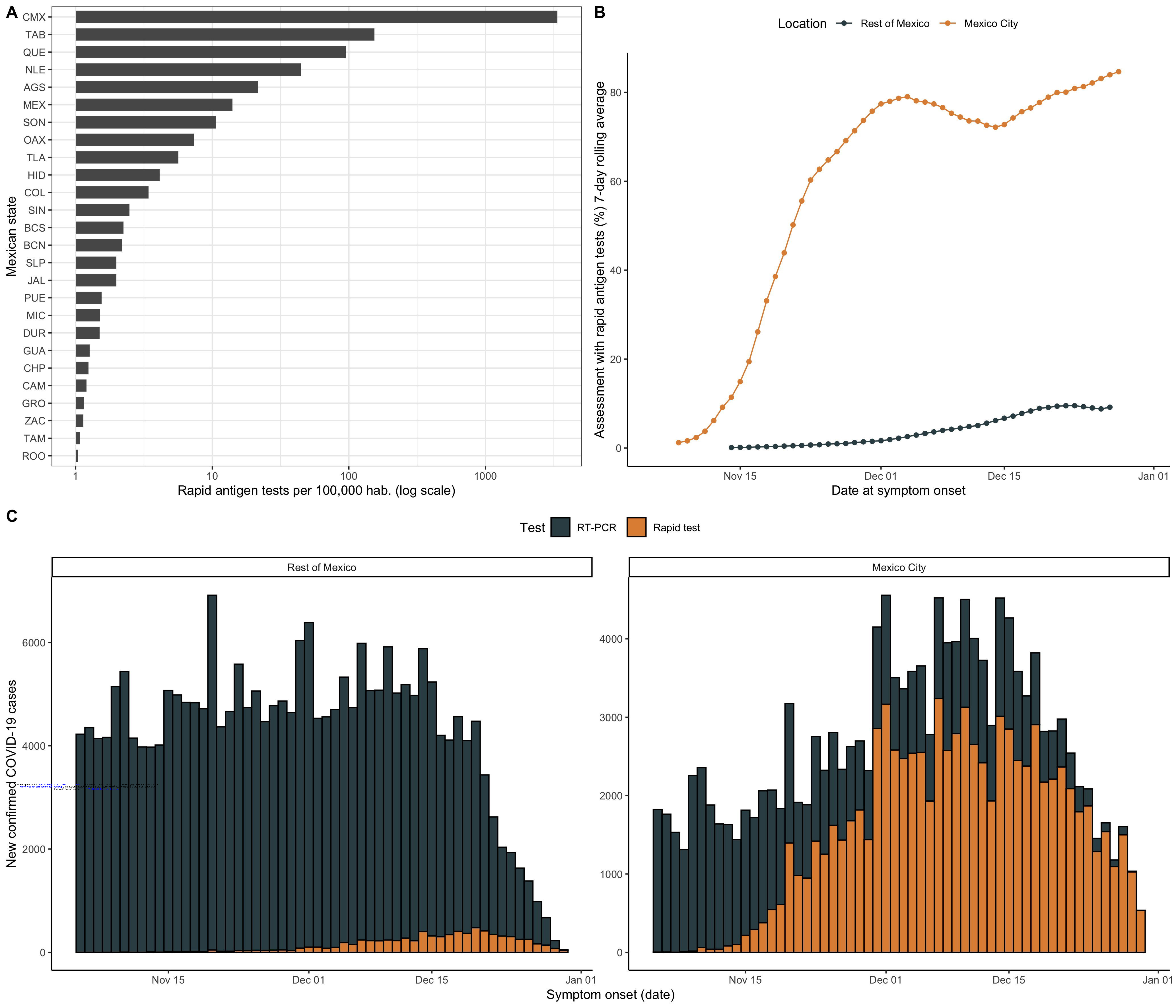


Figure 3. Models assessing risk associated to confusion matrix categories in rapid antigen test results compared to RT-PCR for COVID-19 outcomes including hospitalization (A), requirement for intubation (B), risk of adverse outcomes (C) and lethality (D).

Abbreviations: RT-PCR: Reverse transcription polymerase chain reaction; CKD, Chronic Kidney Disease; CVD: cardiovascular disease; COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; HR: Hazard ratio; 95%CI: 95% Confidence interval; HC: Healthcare.


A
Mexican state
CMX
TAB
QUE
NLE
AGS
MEX
SON
OAX
TLA
HID
COL
SIN
BCS
BCN
SLP
JAL
PUE
MIC
DUR
GUA
CHP
CAM
GRO
ZAC
TAM
ROO
1
10
100
1000
Rapid antigen tests per 100,000 hab. (log scale)
B
Location
Rest of Mexico
Mexico City
Assessment with rapid antigen tests (%) 7-day rolling average
0
20
40
60
80
Nov 15
Dec 01
Dec 15
Jan 01
Date at symptom onset
C
Test
RT-PCR
Rapid test
Rest of Mexico
Mexico City
New confirmed COVID-19 cases
0
2000
4000
6000
0
1000
2000
3000
4000
Nov 15
Dec 01
Dec 15
Jan 01
Symptom onset (date)


A
False Negative Predictors for Rapid Antigen Test in Mexico
CKD
Asthma
Obesity
Smoking Status
CVD
Inmunosupression
COPD
Hypertension
Diabetes
Male Sex
≥7 days Since Symptoms Onset
Age
$\hat{\beta} = 0.54,\ z = -2.79,\ p = 0.005$
$\hat{\beta} = 1.25,\ z = 1.24,\ p = 0.215$
$\hat{\beta} = 0.8,\ z = -2.97,\ p = 0.003$
$\hat{\beta} = 1.15,\ z = 1.61,\ p = 0.107$
$\hat{\beta} = 0.88,\ z = -0.56,\ p = 0.574$
$\hat{\beta} = 0.54,\ z = -2.11,\ p = 0.035$
$\hat{\beta} = 1.15,\ z = 0.5,\ p = 0.616$
$\hat{\beta} = 0.9,\ z = -1.39,\ p = 0.165$
$\hat{\beta} = 1.15,\ z = 1.7,\ p = 0.089$
$\hat{\beta} = 0.86,\ z = -2.95,\ p = 0.003$
$\hat{\beta} = 1.69,\ z = 8.4,\ p = 4.32e-17$
$\hat{\beta} = 0.79,\ z = -8.41,\ p = 4.17e-17$
0.3
1.0
3.0
10.0
Random Effect Logistic Regression Model; OR (95% CI)
AIC = 9598, BIC = 9696
B
False Positive Predictors for Rapid Antigen Test in Mexico
CKD
Asthma
Obesity
Smoking Status
CVD
Inmunosupression
COPD
Hypertension
Diabetes
Male Sex
≥7 days Since Symptoms Onset
Age
$\hat{\beta} = 0.29,\ z = -1.83,\ p = 0.068$
$\hat{\beta} = 0.93,\ z = -0.24,\ p = 0.813$
$\hat{\beta} = 1.02,\ z = 0.11,\ p = 0.911$
$\hat{\beta} = 1.07,\ z = 0.43,\ p = 0.668$
$\hat{\beta} = 0.43,\ z = -1.67,\ p = 0.096$
$\hat{\beta} = 1.46,\ z = 0.77,\ p = 0.439$
$\hat{\beta} = 1.32,\ z = 0.51,\ p = 0.607$
$\hat{\beta} = 0.96,\ z = -0.21,\ p = 0.830$
$\hat{\beta} = 1.19,\ z = 0.96,\ p = 0.338$
$\hat{\beta} = 1,\ z = 0.05,\ p = 0.962$
$\hat{\beta} = 0.94,\ z = -0.38,\ p = 0.701$
$\hat{\beta} = 1.17,\ z = 2.79,\ p = 0.005$
0.1
1.0
10.0
Random Effect Logistic Regression Model; OR (95% CI)
AIC = 3542, BIC = 3644

A
Risk for Hospitalization in Subjects Tested for PCR/Rapid Antigen Test in Mexico
Age
β̂ = 1.72, z = 24.08, p = 0e+00
β̂ = 1.34, z = 6.67, p = 2.54e-11
Male Sex
Number of Comorbidities
β̂ = 1.11, z = 5.3, p = 1.15e-07
Private HC
β̂ = 1.67, z = 2.47, p = 0.013
True-Positive
β̂ = 1.89, z = 11.23, p = 0e+00
False-Negative
β̂ = 1.16, z = 2.68, p = 0.007
β̂ = 1.79, z = 5.06, p = 4.24e-07
False-Positive
1
3
10
Cox Proportional Hazards Regression Model with Frailty penalty function; HR (95% CI)
AIC = 36322, BIC = 37359
B
Mechanical Ventilation Support Odds in Subjects Tested for PCR/Rapid Antigen Test in Mexico
Age
β̂ = 0.86, z = −1.83, p = 0.068
Male Sex
β̂ = 1.34, z = 1.5, p = 0.133
β̂ = 1.16, z = 1.79, p = 0.073
Number of Comorbidities
β̂ = 1.22, z = 0.3, p = 0.761
Private HC
True-Positive
β̂ = 0.87, z = −0.59, p = 0.557
False-Negative
β̂ = 0.47, z = −2.78, p = 0.005
β̂ = 2.29, z = 2.42, p = 0.016
False-Positive
0.3
1.0
3.0
10.0
Random Effect Logistic Regression Model; OR (95% CI)
AIC = 952, BIC = 1003
C
Risk for Severe Outcome in Subjects Tested for PCR/Rapid Antigen Test in Mexico
Age
β̂ = 2.18, z = 17.71, p = 0e+00
Male Sex
β̂ = 1.56, z = 5.2, p = 2.05e-07
Number of Comorbidities
β̂ = 1.18, z = 4.78, p = 1.79e-06
Private HC
β̂ = 2.22, z = 2.36, p = 0.018
True-Positive
β̂ = 3.16, z = 10.29, p = 0e+00
β̂ = 1.27, z = 1.96, p = 0.050
False-Negative
β̂ = 3.06, z = 5.63, p = 1.82e-08
False-Positive
1
3
10
Cox Proportional Hazards Regression Model with Frailty penalty function; HR (95% CI)
AIC = 9431, BIC = 9735
D
Risk for Letality in Subjects Tested for PCR/Rapid Antigen Test in Mexico
Age
β̂ = 2.61, z = 19.15, p = 0e+00
β̂ = 1.5, z = 4.34, p = 1.43e-05
Male Sex
β̂ = 1.15, z = 3.71, p = 2.09e-04
Number of Comorbidities
β̂ = 1.95, z = 1.64, p = 0.101
Private HC
True-Positive
β̂ = 4.41, z = 11.03, p = 0e+00
False-Negative
β̂ = 1.86, z = 4.38, p = 1.16e-05
β̂ = 2.85, z = 4.14, p = 3.42e-05
False-Positive
1
3
10
Cox Proportional Hazards Regression Model with Frailty penalty function; HR (95% CI)
AIC = 7516, BIC = 7743