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SARS-CoV-2 infection and mortality during the first epidemic wave in Madurai, south India: a prospective, active surveillance study

Ramanan Laxminarayan, Chandra Mohan B, Vinay T G, K V Arjun Kumar, Brian Wahl, Joseph A Lewnard

Summary

Background SARS-CoV-2 has spread substantially within India over multiple waves of the ongoing COVID-19 pandemic. However, the risk factors and disease burden associated with COVID-19 in India remain poorly understood. We aimed to assess predictors of infection and mortality within an active surveillance study, and to probe the completeness of case and mortality surveillance.

Methods In this prospective, active surveillance study, we used data collected under expanded programmatic surveillance testing for SARS-CoV-2 in the district of Madurai, Tamil Nadu, India (population of 3 266 000 individuals). Prospective testing via RT-PCR was done in individuals with fever or acute respiratory symptoms as well as returning travellers, frontline workers, contacts of laboratory-confirmed COVID-19 cases, residents of containment zones, patients undergoing medical procedures, and other risk groups. Standardised data collection on symptoms and chronic comorbid conditions was done as part of routine intake. Additionally, seroprevalence of anti-SARS-CoV-2 immunoglobulin G was assessed via a cross-sectional survey recruiting adults across 38 clusters within Madurai District from Oct 19, 2020, to Nov 5, 2020. We estimated adjusted odds ratios (aORs) for positive RT-PCR results comparing individuals by age, sex, comorbid conditions, and aspects of clinical presentation. We estimated case-fatality ratios (CFRs) over the 30-day period following RT-PCR testing stratified by the same variables, and adjusted hazard ratios (aHRs) for death associated with age, sex, and comorbidity. We estimated infection-fatality ratios (IFRs) on the basis of age-specific seroprevalence.

Findings Between May 20, 2020, and Oct 31, 2020, 13·5 diagnostic tests were done per 100 inhabitants within Madurai, as compared to 7·9 tests per 100 inhabitants throughout India. From a total of 440 253 RT-PCR tests, 15 781 (3·6%) SARS-CoV-2 infections were identified, with 8720 (5·4%) of 160 273 being positive among individuals with symptoms, and 7061 (2·5%) of 279 980 being positive among individuals without symptoms, at the time of presentation. Estimated aORs for symptomatic RT-PCR-confirmed infection increased continuously by a factor of 4·3 from ages 0–4 years to 80 years or older. By contrast, risk of asymptomatic RT-PCR-confirmed infection did not differ across ages 0–44 years, and thereafter increased by a factor of 1·6 between ages 45–49 years and 80 years or older. Seroprevalence was 40·1% (95% CI 35·8–44·6) at age 15 years or older by the end of the study period, indicating that RT-PCR clinical testing and surveillance testing identified only 1·4% (1·3–1·6%) of all infections in this age group. Among RT-PCR-confirmed cases, older age, male sex, and history of cancer, diabetes, other endocrine disorders, hypertension, other chronic circulatory disorders, respiratory disorders, and chronic kidney disease were each associated with elevated risk of mortality. The CFR among RT-PCR-confirmed cases was 2·4% (2·2–2·6); after age standardisation. At age 15 years or older, the IFR based on reported deaths was 0·043% (0·039–0·049), with reported deaths being only 11·0% (8·2–14·5) of the expected count.

Interpretation In a large-scale SARS-CoV-2 surveillance programme in Madurai, India, we identified equal risk of asymptomatic infection among children, teenagers, and working-age adults, and increasing risk of infection and death associated with older age and comorbidities. Establishing whether surveillance practices or differences in infection severity account for gaps between observed and expected mortality is of crucial importance to establishing the burden of COVID-19 in India.

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For the Hindi translation of the abstract see Online for appendix 1

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Introduction

By June 10, 2021, more than 29 million confirmed cases of COVID-19 were reported in India, representing the second-highest total of any country after the USA.[1] Although India has reported 354 000 COVID-19 deaths, this substantial burden nonetheless represents a lower overall fraction of fatal cases than other settings have shown.[2,3] Hypotheses addressing this apparent gap have

Research in context

Evidence before this study

Characterising risk factors associated with infection, disease severity, and mortality in low-income and middle-income countries (LMICs) can help inform treatment and prevention efforts, including optimal vaccine allocation strategies.

We searched PubMed from inception to June 1, 2021 to identify English-language studies examining risk factors associated with SARS-CoV-2 infection and mortality that had appropriate comparator populations or methods to account for potential confounding factors. We used the search terms "COVID-19", "SARS-CoV-2", or "novel coronavirus" and "risk factors", "predictor", "determinant", "mortality", "fatality", or "IFR" together with search criteria proposed by the Cochrane Library to identify studies relevant to LMICs. One study from north India used clinical data comprising individuals seeking care or diagnosis at a health facility and identified that increasing age, male sex, and hypothyroidism increased the odds of SARS-CoV-2 infection. Several studies reported on predictors of mortality among individuals admitted to hospital, including studies published in Brazil, China, India, Iran, and South Africa, and multicountry studies across sub-Saharan African research consortia. In general, these studies report that increasing age, male sex, and several comorbidities (ie, diabetes, obesity, and hypertension) are associated with increased risk of death, consistent with findings in high-income countries. However, all studies were limited by reliance on convenience sampling in clinical settings. None of the studies differentiated outcomes of symptomatic or asymptomatic infection, and none used community-based surveillance efforts to assess predictors of infection and mortality. Several studies have used community-based seroprevalence surveys in Indian cities or states to estimate infection-fatality ratios (IFRs), generally in ranges of less than 0·1%. However, the reasons for the difference in IFR estimates relative to other countries remain uncertain.

Added value of this study

Our study used data from a large-scale surveillance study in Madurai district, Tamil Nadu, south India to characterise risk factors for infection (ie, symptomatic and asymptomatic) and mortality, and to probe the completeness of epidemiological reporting. We observed increased odds of symptomatic infection among men and older age groups and among individuals with comorbid conditions (ie, diabetes, hypertension, and respiratory disorders). By contrast, risk for asymptomatic infection did not differ among children and young adults, but increased at ages 40 years and older.

We also observed that older age, male sex, and a history of cancer, diabetes, chronic kidney disease, hypertension, other chronic circulatory disorders, respiratory disorders, and endocrine disorders were each independently associated with higher risk of COVID-19 mortality. After age standardisation, we identified higher risk of mortality among patients in Madurai than those in the USA, Europe, China, and South Korea, suggesting surveillance in Madurai captured a more severe clinical spectrum of cases; in conjunction, we estimated that only 1·4% of infections were ascertained by surveillance.

We further identify that only 11% of deaths among individuals aged at least 15 years and older, which would be expected on the basis of seroprevalence in Madurai and IFR estimates from other settings, were ascertained by surveillance.

Implications of all the available evidence

The findings of this study and previous studies could help clinicians to identify patients who are at elevated risk of severe COVID-19 disease in settings in which resources are limited. In addition, a more complete understanding of risk factors could inform COVID-19-vaccine allocation strategies in India and other LMICs now that effective vaccines are available. Investigations of all-cause and cause-specific deaths in India during the COVID-19 pandemic are warranted given the considerable discrepancy between observed and expected deaths in this setting.

surrounded both the younger age distribution of India's population[4] and possible undercounting of deaths attributable to COVID-19, which has been reported in other low-income and middle-income countries.[5,6] However, large-scale studies of SARS-CoV-2 infection and mortality in India are scarce, hindering efforts to compare COVID-19 epidemiology against observations in other settings.

Under India's decentralised health system, administrative divisions customarily adapt national programmes and guidelines for local contexts. Madurai, a city and administrative district in Tamil Nadu, was the site of an augmented, population-based surveillance programme modelled after examples in other settings.[7,8] Efforts included house-to-house syndromic surveillance and testing, expanded asymptomatic testing in clinical and community settings, establishment of fever clinics, monitored isolation of cases, and cross-sectional antibody serosurveillance. Here we report on findings of this expanded programme throughout the first wave of the COVID-19 epidemic during summer 2020, including risk factors for infection and mortality, and comparisons of reported deaths against observations from other settings.

Methods

Study setting

The Office of the Deputy Director of Health of Madurai District enacted coordinated, enhanced surveillance protocols involving all public-sector and private-sector clinical care providers in the district. With a population of

1734000 in 2020 (and 3266000 within the administrative district), Madurai is the third-largest city in Tamil Nadu and was the geographical focus of a distinct wave of the COVID-19 epidemic during June and July, 2020, in southern Tamil Nadu, following the initial incursion of the epidemic in Chennai.[4] Although not the wealthiest state in India, Tamil Nadu has effective public health and health-care delivery systems, and ranks among the top Indian states in per-capital health-care workers and total-health expenditures.[9]

RT-PCR testing

Tamil Nadu exclusively authorised RT-PCR testing for SARS-CoV-2 during the pandemic, facilitating centralised monitoring by the state's Department of Health and Family Welfare of all tests administered and results processed by both public-sector and private-sector laboratories. Consistent with the Indian Council of Medical Research (ICMR) guidelines,[10] testing was indicated for all patients who presented to health-care facilities and met the WHO case definitions for influenza-like illness (fever of ≥38°C and cough with onset within 10 days) or severe acute respiratory illness (cases meeting criteria for influenza-like illness and requiring hospital admission). In Madurai, RT-PCR testing was further recommended for individuals with any other symptoms potentially associated with COVID-19. Standardised reporting forms (SRFs) administered with each test addressed the presence of fever, respiratory symptoms, pharyngitis, myalgia, and gastroenteritis, and patients' history of diagnosis of comorbid conditions, on the basis of self-reporting or (if available) provider records.

Additionally, RT-PCR testing was indicated for individuals receiving inpatient care for other causes at hospitals. Testing was done at the time of hospital admission (due to any cause) in patients aged at least 65 years, those who were immunocompromised, patients with known chronic comorbid conditions, and other patients in high-risk groups such as transplant patients and those with malignancy (current or previous). Testing was further indicated for all patients who were having invasive procedures (surgical or non-surgical), and pregnant women admitted to hospital for delivery.

Community-health workers did risk-based active surveillance testing through door-to-door canvassing. Testing was indicated for all individuals who had influenza-like illness within containment zones (areas ranging in size from a city block to a ward or neighbourhood with concurrent cases across several households), and elsewhere prioritised individuals who had influenza-like illness and who had known contact with a laboratory-confirmed case, who had travelled abroad (within 14 days) or outside Tamil Nadu (within 7 days), or who participated in frontline work in health-care, containment, or mitigation activities. Both inside and outside containment zones, testing was indicated for all asymptomatic individuals who had physical contact or high-risk social contact (eg, household or workplace exposure lasting ≥15 min) with confirmed cases within the past 5–10 days. Within containment zones, testing was further indicated for all individuals who were elderly, immunocompromised, or had known comorbidities. Outside containment zones, such individuals were recommended to receive tests within 5–10 days of any contact with known cases.

Patients' symptoms, age, sex, known comorbid conditions or immunocompromised status, residence within or outside of a containment zone, frontline occupation, and recent history of travel or contact with a confirmed COVID-19 case, and other indications for testing were recorded on the SRFs (adapted from the ICMR form), which were submitted electronically to the state health ministry with each RT-PCR test order. Hospital or other health-care facility-based isolation was initially recommended by ICMR for all patients with laboratory-confirmed infection; although this directive was later relaxed nationwide, facility-based isolation of patients with COVID-19 continued throughout the study period in Madurai for 99·6% of confirmed cases. Symptoms experienced during facility-based isolation were recorded and submitted to the health ministry via a separate standardised electronic form at the time of patient death or discharge.

Serosurveillance

As part of a state-wide cross-sectional serosurvey,[11] 38 random GPS points, generated by a computer as random latitude and longitude coordinates, were selected within distinct health-unit divisions (administrative subunits) of Madurai district, with the aim of allocating roughly ten points per million inhabitants. Surveyors approached households adjacent to each selected point aiming to enrol one participant aged at least 18 years per household, until 30 individuals were enrolled within a cluster. Within households opting to participate, a single member was selected to enrol at random, on the basis of their age using the Kish method.[12] Participants completed a health questionnaire and provided 5 mL of blood by venipuncture. Presence of reactive IgG against the SARS-CoV-2 spike protein was assessed using a commercial chemiluminescence assay (iFlash-SARS-CoV-2 IgG; Shenzhen YHLO Biotech, Shenzhen, China; sensitivity 95·9% and specificity 95·7% according to the manufacturer; sensitivity 93·0% and specificity 92·9% according to independent assessment).[13] Serosurvey enrolment proceeded from Oct 19, 2020, to Nov 5, 2020.

Statistical analysis

We estimated adjusted odds ratios (aORs) and accompanying 95% CIs using conditional logistic-regression models to identify factors predicting positive RT-PCR results among all people tested. Models included age (aggregated into 5-year groupings), sex, and reported comorbid conditions as risk factors; models also included symptoms reported at the time of testing to identify aspects

of clinical presentation, documented at the time of testing, independently associated with SARS-CoV-2 detection. To mitigate confounding, we defined analysis strata on the basis of calendar week and all applicable testing indications, including history of travel, history of contact with a confirmed case, frontline work, inpatient admission or medical procedure screening for causes other than severe acute respiratory illness, and residence in a containment zone. Unique strata were defined for each combination of criteria, within each week, to account for differences in pre-test probability of a positive result among individuals under varying testing indications and over time.

Using the same modeling framework, we sought to estimate the aOR of each risk factor with outcomes of symptomatic or asymptomatic SARS-CoV-2 infection, defined according to presence of symptoms at the time of testing or at any subsequent point throughout the course of clinical follow-up. We considered individuals with negative tests without reported symptoms as a reference group for both analyses to enable comparison of effect-size estimates, and to mitigate confounding from associations of each predictor with other causes of acute febrile or respiratory illness.

We estimated adjusted risk ratios (aRRs) and accompanying 95% CIs for anti-SARS-CoV-2 IgG detection among serosurvey participants via Poisson regression. We used the sandwich estimator to compute robust standard errors addressing correlation within survey clusters. Models included participant age, sex, history of contact with a known COVID-19 case, presence of any chronic comorbid condition or immunocompromised status, frontline occupation, and calendar date (to ensure seroprevalence did not differ among participants according to enrolment dates). A quadratic transformation of age was found to provide an optimal penalised fit, relative to linear or higher-order polynomial terms, by the Bayesian information criterion.

To estimate seroprevalence among all adults, we reweighted age-specific seroprevalence estimates according to the population of Madurai district in 2020, within 5 year strata. We estimated total infections via the sum of the products of seroprevalence and population size across age groups. We estimated the proportion of all infections identified through RT-PCR testing by dividing total reported cases to Oct 19, 2020, by total estimated infections.

We computed 30-day case fatality risk (CFR) among RT-PCR-confirmed COVID-19 cases from the date of testing, stratifying by age group (<40 years, 40–64 years, 65–79 years, and ≥80 years), sex, and known comorbidities, including diabetes, hypertension, and other circulatory disorders, chronic kidney disease, respiratory disorders (including asthma with or without wheeze, chronic obstructive pulmonary disease, history of tuberculosis, or other conditions), other non-diabetes endocrine disorders, and cancer. We computed 95% CIs via bootstrap resampling.

To ascertain risk factors for death among RT-PCR-confirmed cases, we estimated adjusted hazard ratios (aHRs) and accompanying 95% CIs for time to death, following RT-PCR testing, according to demographic and clinical factors including age group, symptoms, and known comorbidities. Cox proportional hazards models accounted for strata by week and by testing indication to mitigate confounding resulting from differences in cases ascertained over time and under differing testing indications, as described in the aforementioned analyses of RT-PCR testing data. We verified the proportional hazards assumption by testing for non-zero slopes of coefficients via Schoenfeld residuals; terms for chronic kidney disease and non-diabetes endocrine disorders were dropped because of violation of this assumption. Estimates of CFRs and aHRs excluded fatal COVID-19 cases identified posthumously or the same day as their death, for whom it was not possible to establish whether posthumous testing was done. Guidelines over the study period included RT-PCR testing of nasal specimens from deceased suspected cases at health-care facilities.

We estimated the infection-fatality ratio (IFR) overall and within 5 year strata among individuals aged at least 15 years by dividing total COVID-19 deaths (defined as deaths occurring by Nov 5, 2020, or at any time among cases diagnosed by Oct 19, 2020) by the estimated total number of infections occurring by Oct 19, 2020. Analyses of IFRs did not exclude deaths recorded posthumously or on the same day as case confirmation.

We first compared the risk of death among RT-PCR-confirmed cases in Madurai against observations from other settings. We identified available data on cases and deaths in standardised 10 year age groups from the USA,[14] England,[15] Italy,[16] South Korea,[17] and China, Hong Kong, and Macau.[18] Defining the age distribution of cases within each of these settings as a reference distribution, we reweighted Madurai cases to replicate the age distribution of the other settings, and compared age-standardised CFR estimates for Madurai cases to CFR estimates from each comparator setting. For the USA[14] and Italy,[19] we further computed standardised CFR estimates reweighted to account for age-specific prevalence of at least one comorbid condition among cases. We generated 95% CIs for CFR estimates via bootstrap resampling.

Next, we compared total reported COVID-19 deaths within Madurai against expectations from IFR estimates in other settings. Pooled, upper-bound, and lower-bound IFR estimates within standardised (5-year) age strata were available from a meta-analysis[20] of studies from Spain, Geneva, New York City, England, Italy, Kenya, Portugal, and Sweden. We computed the expected number of deaths among all infections occurring by Oct 19, 2020, in Madurai in people aged 15 years or older by multiplying age-specific total infections in Madurai by age-specific IFR estimates from these other settings (pooled, upper bound, and lower bound estimates).[20] We

	All individuals		Symptoms reported*		Symptoms not reported	
	Total tested	Infected	Total tested	Infected	Total tested	Infected
Travel	72 270	844 (1·2%)	18 293	468 (2·6%)	53 977	376 (0·7%)
Known contact	111 324	5141 (4·6%)	17 440	1337 (7·7%)	93 884	3804 (4·1%)
Frontline workers	21 106	589 (2·8%)	16 163	447 (2·8%)	4943	142 (2·9%)
Medical procedure screening or inpatient admission	19 817	576 (2·9%)	19 817	576 (2·9%)	8308	260 (3·1%)
Containment-zone residents	29 157	985 (3·4%)	18 212	781 (4·3%)	10 945	205 (1·9%)
Symptomatic illness at time of testing	162 884	8720 (5·4%)	162 884	8720 (5·4%)	NA	NA
Voluntary self-referral	77 938	1420 (1·8%)	812	137 (16·9%)	77 126	1283 (1·7%)
Indication not reported	42 372	1269 (3·0%)	NA	NA	42 372	1269 (3·0%)
All tests administered†	440 253	15 781 (3·6%)	162 884	8720 (5·4%)	279 980	7061 (2·5%)

Data are N or n (%). NA=not applicable. *New-onset symptoms reported after RT-PCR testing among confirmed cases are reported in the appendix 2 (p 3). †The sum of tests administered across listed categories is not equal to all tests administered because individuals might have met several criteria for testing. Attributes of people tested and cases diagnosed, by testing indication, are detailed in the appendix 2 (pp 4–13).

Table: **SARS-CoV-2 detection across RT-PCR testing strata**

See Online for appendix 2

divided observed deaths by this value to obtain the ratio of observed-to-expected mortality in Madurai.

Ethical approval

Primary-data collection was done as public health surveillance. Secondary-data analyses summarised in this report were considered to be exempt from review by review boards at the investigators' institutions.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 20, 2020, and Oct 31, 2020, 440 253 RT-PCR tests identified 15 781 (3·6%) SARS-CoV-2-positive cases (table; figure 1). Overall, 162 884 (37·0%) of 440 253 tests were administered to individuals with symptoms at the point of testing, with 148 490 (33·7%) of 440 253 tests being done in people who met the case definition for influenza-like illness or severe acute respiratory illness. 8720 (5·4%) of 162 884 tests were positive in individuals with any type of symptoms, 6831 (4·6%) of 148 490 were positive in individuals with influenza-like illness or severe acute respiratory illness, and 7061 (2·5%) of 279 980 were positive in individuals without symptoms. Throughout clinical follow-up, symptoms were recorded for 2597 (36·8%) of 7061 RT-PCR-confirmed cases without reported symptoms at the time of testing (appendix 2 p 3). We indicate differences in populations reached and cases identified across testing categories in appendix 2 (pp 4–14).

Testing the 111 324 contacts of known cases with RT-PCR identified 5141 (4·6%) cases of COVID-19. About 3% of frontline workers, high-risk containment-zone residents, and individuals screened for medical procedures or admitted to hospital for non-severe acute respiratory-illness conditions tested positive (table). Among individuals screened for SARS-CoV-2 infection because of recent travel, 468 (2·6%) of the 18 293 who had symptoms and 376 (0·7%) of the 53 977 who did not have symptoms tested positive.

Adjusted odds of a positive RT-PCR test result were 9% (95% CI 5–12) higher among male than female individuals, and generally increased with age, such that the adjusted odds of a positive test result were 1·89 (95% CI 1·50–2·35) times higher in people aged 80 years or older than in those aged 0–4 years (figure 2). Adjusted odds of symptomatic SARS-CoV-2 infection were 21% (16–25) higher among male than female individuals, whereas this difference was reversed for asymptomatic infection. Individuals aged 80 years or older had 4·35 (3·18–6·00) times higher adjusted odds of symptomatic RT-PCR-confirmed infection than individuals aged 0–4 years. By contrast, the aOR for asymptomatic infection among individuals aged at least 80 years versus those aged 0–4 years was 2·10 (1·49–2·93). Adjusted odds of asymptomatic RT-PCR-confirmed infection did not differ across ages 0–44 years, but stepwise increases in aOR estimates were apparent with nearly every 5 year increment in age thereafter.

Comorbidities associated with higher odds of SARS-CoV-2 detection by RT-PCR, irrespective of symptoms, included diabetes, hypertension and other circulatory disorders, cancer, and respiratory disorders (appendix 2 p 15). Specific symptoms reported at presentation and during follow-up among individuals with RT-PCR-confirmed infection are provided (appendix 2 pp 3 and 15).

1140 adults aged 18–84 years (30 participants per cluster) were enrolled in the serosurvey, among whom 451 (39·6%) had reactive IgG results (figure 3; appendix 2 pp 3 and 24). Probability of antibody detection did not vary over time during the serosurvey. Overall estimated seroprevalence in people aged at least 15 years was 40·1% (95% CI 35·8–44·6) by the end of the study period, corresponding to 1·05 (95% CI 0·94–1·17) million infections. With 14 736 RT-PCR-confirmed cases within this age group, surveillance testing was estimated

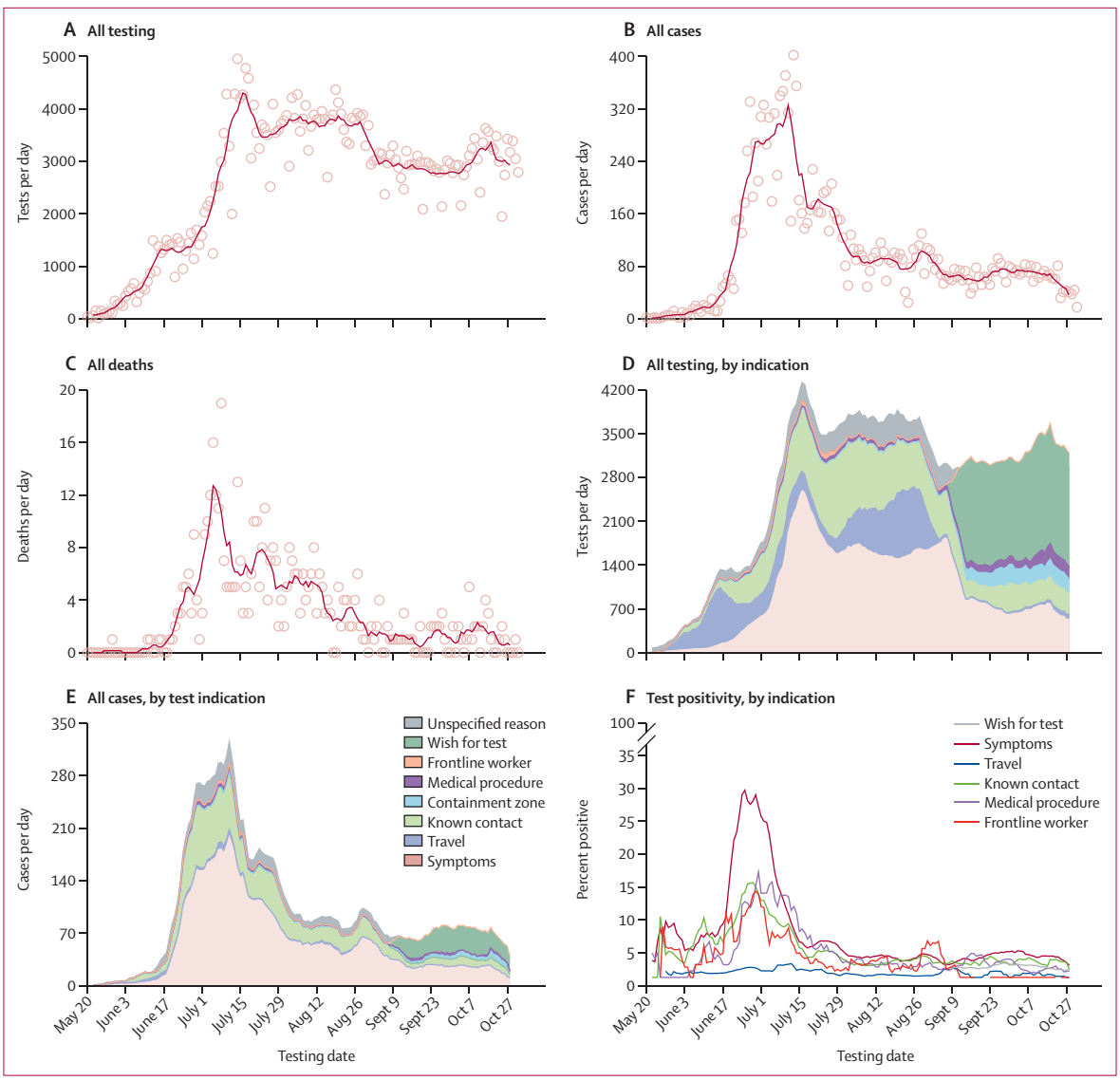

Figure 1: **Time series of RT-PCR testing, SARS-CoV-2 detection, and mortality in Madurai, in May, 2020, to October, 2020**
Numbers of SARS-CoV-2 tests done per day (A), COVID-19 cases detected per day (B), and COVID-19 deaths (C; points) along with 7 day moving-average values (lines) per day. Stratified 7 day moving-average values of the number of tests done (D), number of cases detected (E), and proportion of tests yielding positive results (F), by testing indication. For individuals without symptoms at the time of testing who met multiple criteria for testing, we assigned a single testing indication at random for the purposes of plotting.

to have captured 1·4% (95% CI 1·3–1·6) of infections in people aged at least 15 years (appendix 2 p 17).

Exposures associated with antibody detection generally resembled risk factors predicting positive RT-PCR results. Serosurvey participants known to have had contact with a person confirmed to have had COVID-19 had a 2·19 (95% CI 1·44–3·25) times higher probability of antibody detection than those without known contact (appendix 2 p 16), and we identified higher probability of antibody detection at older ages (figure 3), although differences by participant sex were not apparent (appendix 2 p 16). Participants reporting any chronic comorbid condition were 32% (1–73) more likely to have reactive IgG-assay results than those without known comorbidities.

Among RT-PCR-confirmed cases tested by Oct 1, 2020, 342 (2·4%; 95% CI 2·2–2·6) of 14237 died within 30 days of their positive test. Mortality was 0·4% (95% CI 0·3–0·6) at ages 0–39 years, 2·0% (1·7–2·3) at ages 40–64 years, 7·5% (6·4–8·7) at ages 65–79 years, and 15·4% (11·6–19·6) in those aged 80 years or older (figure 4). Among male individuals mortality was 2·9% (2·5–3·3) and among female individuals was 1·7% (1·4–2·0). Among people with at least one comorbid condition, mortality was 5·7% (5·1–6·4), compared with 0·7% (0·5–0·8) in those without any comorbid condition; we present stratified

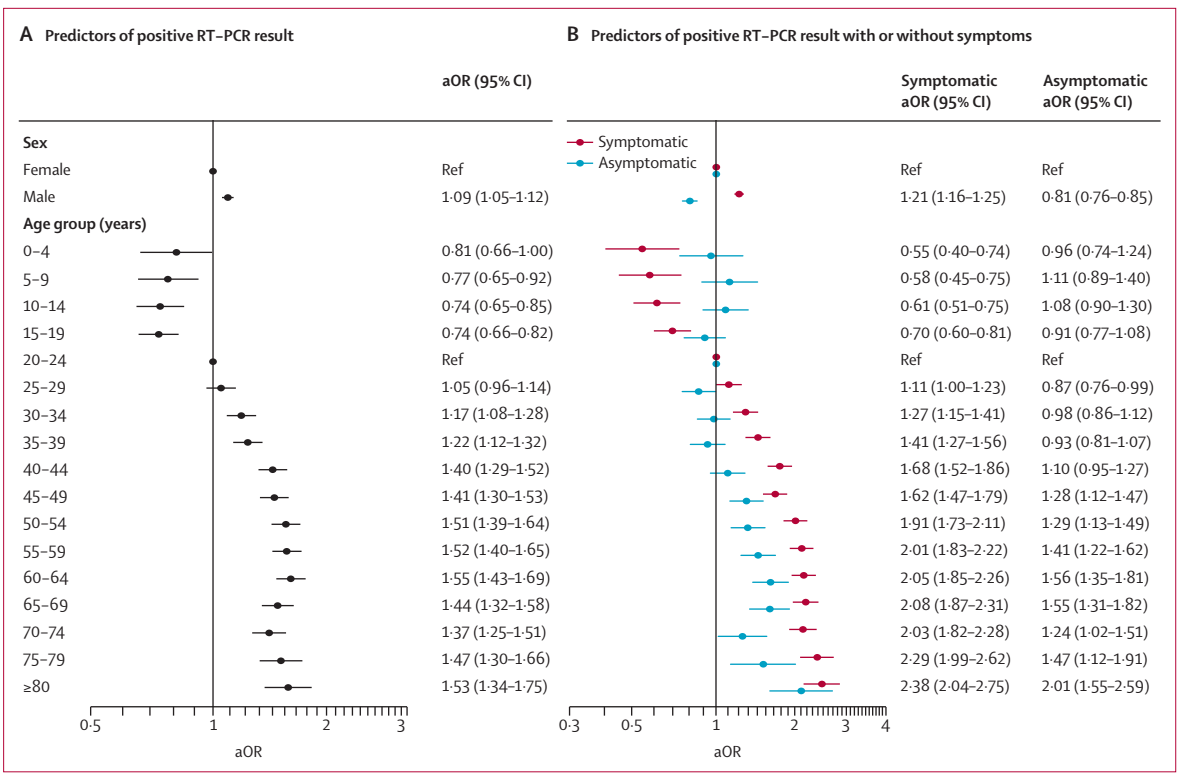

Figure 2: **Demographic predictors of infection**
Estimates of the aOR for SARS-CoV-2 detection (A), and symptomatic or asymptomatic SARS-CoV-2 detection (B), on the basis of conditional logistic-regression models stratified for time and testing indication. Lines indicate 95% CIs around maximum-likelihood point estimates. aOR=adjusted odds ratio.

estimates for individual and paired comorbid conditions (figure 5). Age, male sex, and presence of comorbid conditions remained predictive of mortality in multivariate-adjusted analyses (appendix 2 pp 18–19). The estimated aHR for mortality among people aged at least 80 years, relative to those aged 15–19 years, was 35·4 (95% CI 2·90–151·3). Higher risk of mortality was independently associated with diabetes (aHR 2·28, 95% CI 1·79–2·91), hypertension (2·08, 1·62–2·66) and other circulatory disorders (3·89, 2·66–5·71), respiratory disorders (4·57, 2·43–8·61), and cancer (8·04, 3·47–18·65). Accounting for total estimated SARS-CoV-2 infections by Oct 19, 2020, the IFR based on reported deaths in individuals aged at least 15 years in Madurai was 0·043% (95% CI 0·039–0·049; figure 6; appendix 2 p 19). The comparison of CFR and IFR in Madurai with other settings is reported in figure 6 and the appendix 2 (pp 19–23).

Discussion

In Madurai, India, comprehensive surveillance programmes encompassing clinical testing and active case finding in the community identified only 1·4% of SARS-CoV-2 infections during the first epidemic wave. Although these programmes yielded 13·5 tests per 100 residents over the study period in Madurai, only 7·9 tests were done per 100 residents across India over the same period.[1] Thus, case data from other parts of the country might underestimate total infections by a wider margin.

Our combined analyses of RT-PCR confirmed cases, mortality, and population seroprevalence raise several considerations about the comprehensiveness of SARS-CoV-2 surveillance data in this setting. Point estimates of the CFR were higher in Madurai than in the USA, England, Italy, South Korea, and China, Hong Kong, and Macau at ages 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, and 50–59 years, but were concordant between Madurai and these other settings at older ages (figure 6).[14–18] Additionally, prevalence of known comorbidities was higher at younger ages in Madurai, India, than in the USA and Italy, and lower at older ages (appendix 2 p 20). After standardising for the age distribution of cases in each comparator setting, people ascertained to have SARS-CoV-2 infection in Madurai had higher mortality than people in the other settings (appendix 2 p 21). Notably, this gap widened after further standardising for age-specific prevalence of at least one comorbid condition when compared with the USA and Italy. Thus, despite extensive testing efforts targeting asymptomatic individuals at high risk, which achieved two-times higher per-capita testing rates in Madurai than in the rest of India, surveillance efforts in Madurai are likely to have captured a more severe spectrum of disease cases.

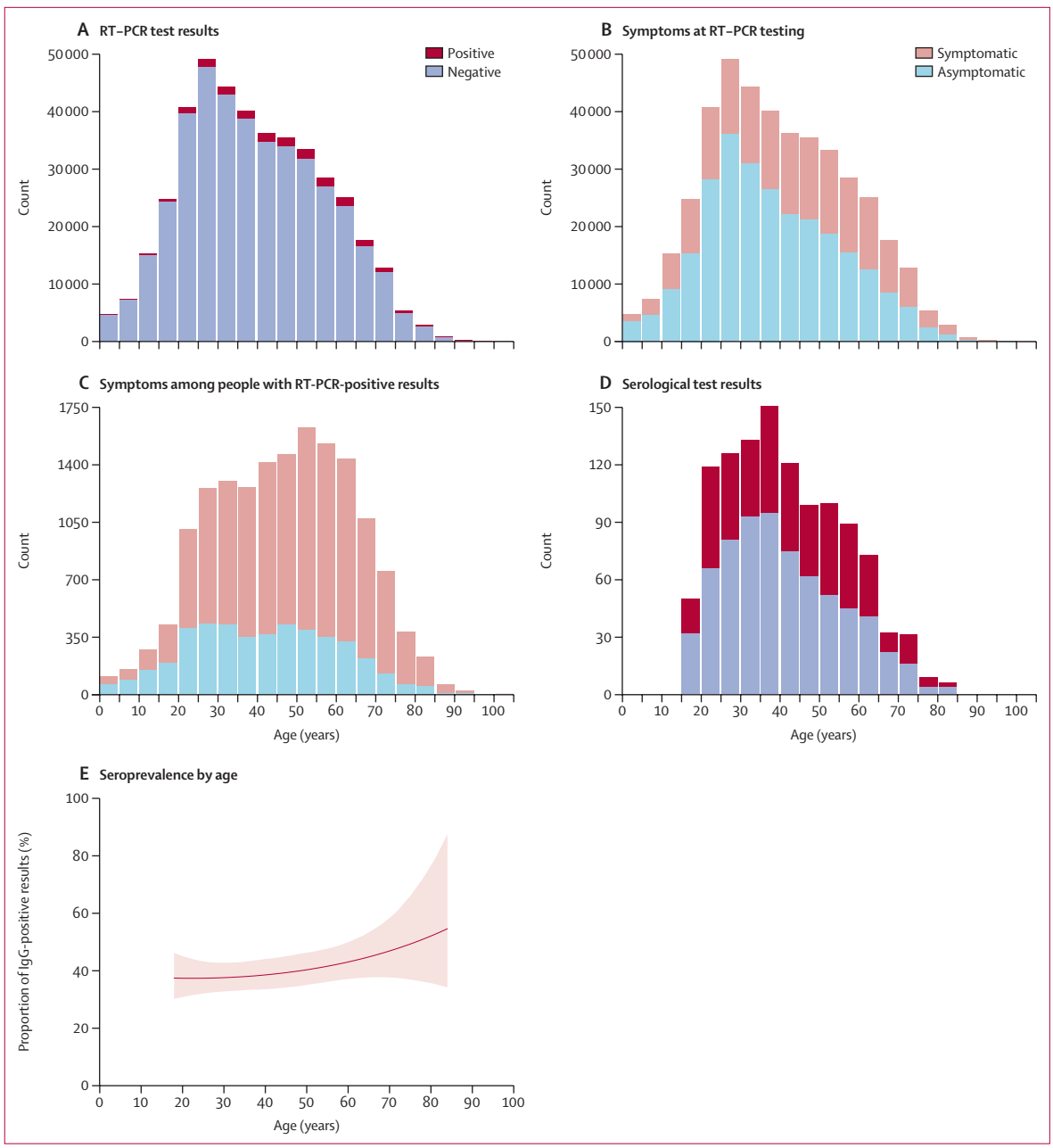

Figure 3: **Infections detected through RT-PCR and serological testing and presence of symptoms among people with RT-PCR-confirmed COVID-19**
Total positive and negative results by age for RT-PCR testing (A), and presence of symptoms at the point of testing for all individuals receiving RT-PCR tests (B) and all those with RT-PCR-confirmed COVID-19 (C). (D) Results of antibody testing. (E) Age-specific seroprevalence; further risk factors for antibody detection are reported in the appendix 2 (p 16). Shaded regions show 95% CIs around maximum-likelihood point estimates (line).

Despite this bias toward ascertainment of more-severe cases in Madurai, our findings further suggest that SARS-CoV-2 mortality might be substantially underestimated in this setting (figure 6). Within each age stratum, IFR point estimates in Madurai were lower than pooled estimates from eight comparator settings comprising both high-resource and low-resource settings;[20] moreover, at ages 40 years or older, IFR estimates in Madurai were lower than lower-bound IFR estimates from these settings. On the basis of pooled IFR estimates from other settings and our estimate of 40·1% SARS-CoV-2 seroprevalence at ages 15 years and older in Madurai, 4164 (95% CI 3146–5538) deaths caused by COVID-19 would be expected to occur over the study period within this age group. With 456 deaths reported in Madurai at ages 15 years or older, the ratio of observed-to-expected mortality was 0·11 (0·08–0·14; appendix 2 pp 22–23). Gaps between observed and expected deaths widened at older

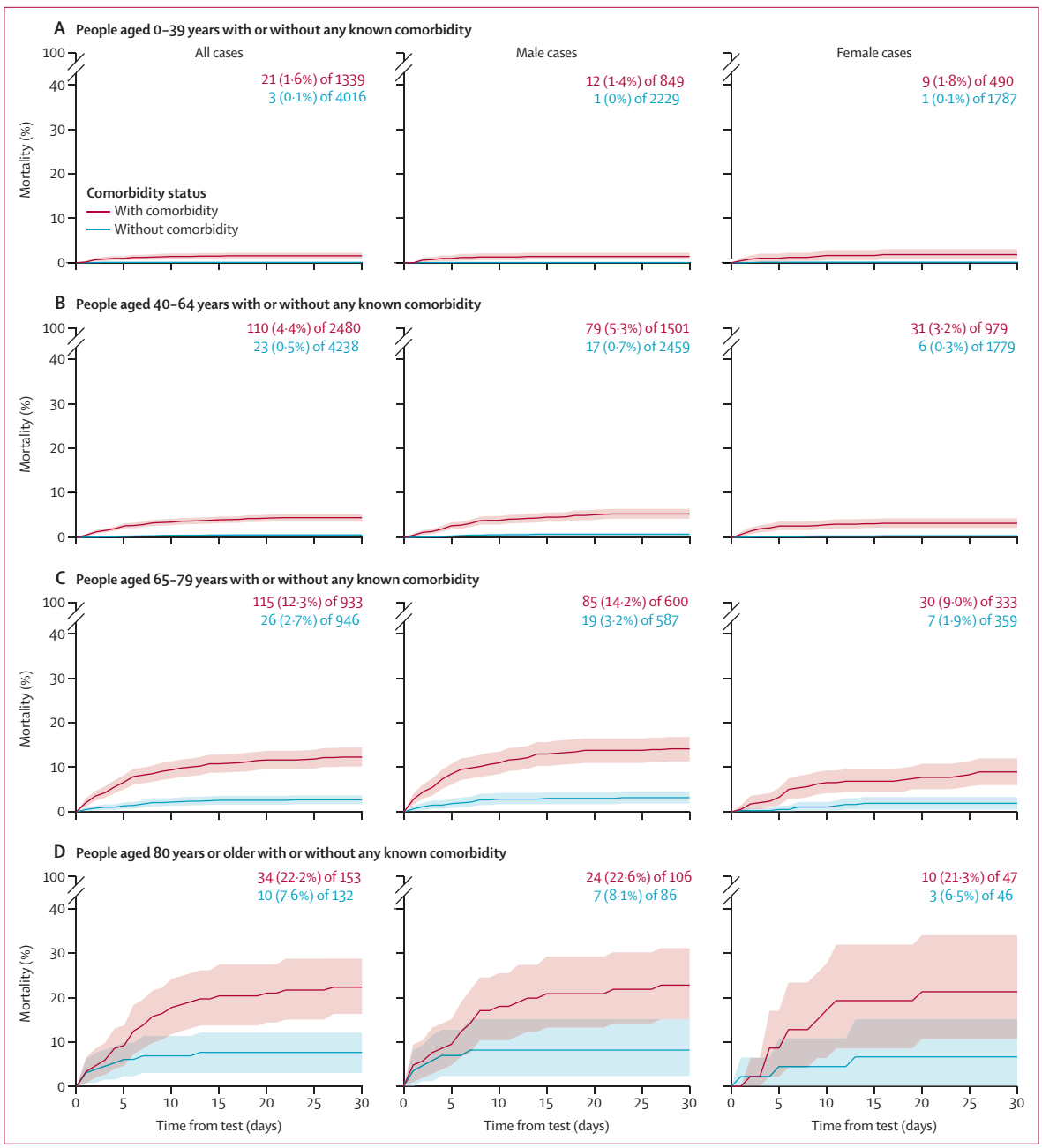

Figure 4: **Risk of death by age, sex, and comorbid conditions**
Proportion of people with RT-PCR-confirmed COVID-19 dying over the 30 days following their testing date, stratified by age and sex, for individuals with (red) and without (blue) at least one known comorbid condition. Shaded areas indicate 95% CIs, generated via bootstrap resampling. Panels include the number and proportion of patients who died among all individuals within 30 days of follow-up.

ages; at ages 80 years or older, the ratio of observed-to-expected deaths was 0·039 (0·023–0·062). Because our IFR estimates based on reported mortality in Madurai are consistent with observations from other studies within India,[21,22] it is essential to establish whether underestimation of deaths or true differences in disease progression among Indian patients explains why only one death was reported for every 9·1 deaths that were expected to occur.

Our study has limitations. Whereas the serosurvey systematically targeted a representative community-based sample, RT-PCR testing access varied over time; thus, data from RT-PCR clinical and surveillance testing do not capture true incidence or prevalence of infection in Madurai. Because potential COVID-19 symptoms collected on SRFs are incomplete, designations of symptomatic or asymptomatic infections might be subject to

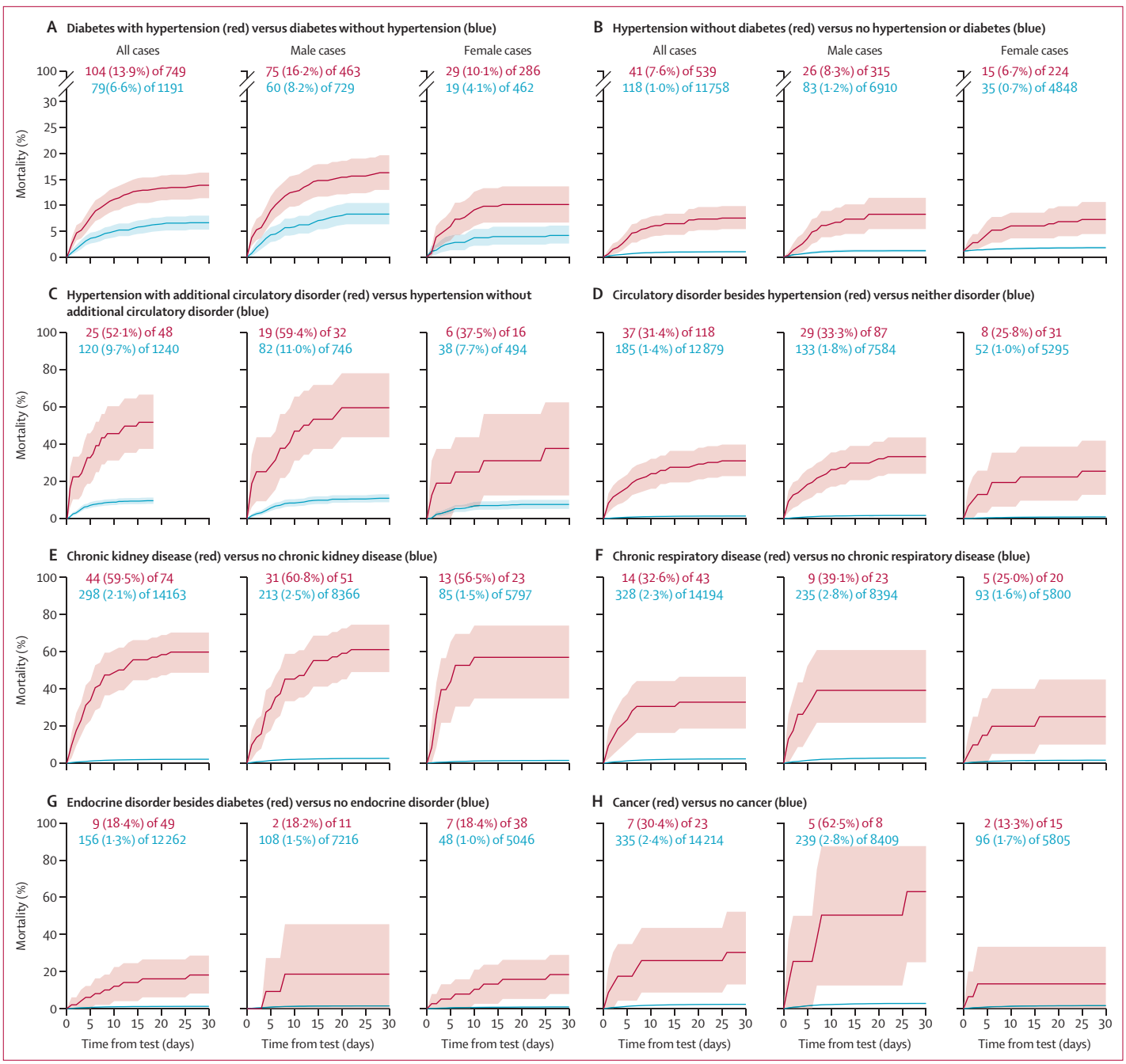

Figure 5: **Risk of death associated with individual comorbid conditions**

30 day mortality risk among people with RT-PCR-confirmed COVID-19 with or without specific comorbidities, stratified by sex, in those with diabetes with or without hypertension (A), hypertension without diabetes (B) or additional circulatory disorders (C–D), chronic kidney disease (E), chronic respiratory disease (F), endocrine disorders other than diabetes (G), and cancer (H). Panels include the number and proportion (in parentheses) of patients who died among all individuals within 30 days of follow-up. Plot labels indicate comparison groups with data presented in red or blue for individuals with or without each comorbid condition of interest.

misclassification, particularly for individuals who did not meet influenza-like illness or severe acute respiratory illness case definitions. Data on comorbid conditions and immune status could also have been incomplete because of substantial underdiagnosis of non-communicable diseases in India, biasing findings toward the null for associations of comorbid conditions with SARS-CoV-2 infection and mortality. Although differences in comorbidity prevalence might also confound comparisons of IFR across settings, previous analyses have suggested minimal quantitative effects of such factors on absolute estimates.[22] Detailed data were not collected on individual

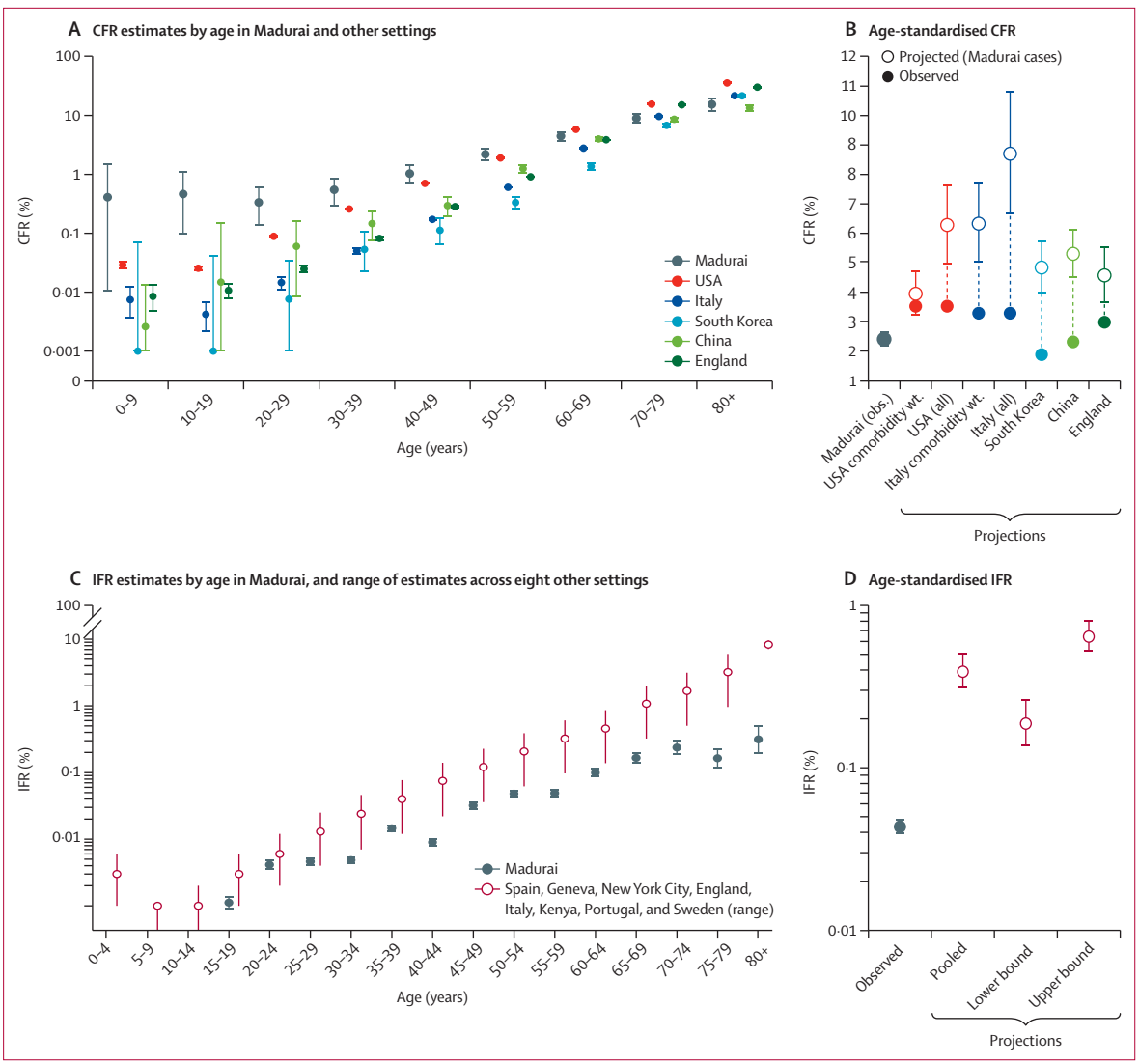

Figure 6: **Comparison of mortality across settings**

(A) Age-specific CFRs for Madurai alongside those for cases in the USA,[14] England,[15] Italy,[16] South Korea,[17] and China, Hong Kong, and Macau.[18] (B) CFRs for Madurai cases standardised to the age distribution of cases in other settings (open points); solid points indicate CFRs observed among cases in each setting. (C) Age-specific IFR estimates in Madurai (black) alongside ranges of IFR estimates across eight settings,[20] and (D) overall IFR estimates for individuals aged at least 15 years in Madurai versus pooled, lower-bound, and upper-bound IFR estimates of the IFR from other settings,[20] standardised for the age distribution of infections in Madurai. Numerical results plotted in this figure are presented in the appendix 2 (pp 19–23). CFR=case-fatality ratio. IFR=infection-fatality ratio. Obs=observed. Wt=weighted.

socioeconomic status, limiting our assessment of factors underlying differential exposure and mortality within the population. Associations of age and comorbidity with infection might differ in settings that enacted differing non-pharmaceutical interventions, including stringent attempts to shield people at greatest risk of severe disease.[23–26] Last, use of antigen-based testing elsewhere within India should be considered when comparing results from exclusive RT-PCR testing in Tamil Nadu with data from other Indian states.

Reasons for lower-than-expected reported COVID-19 mortality in Madurai and other parts of India[21,22] merit further investigation. Although cross-protective immunity from non-SARS-CoV-2 coronavirus infections has been suggested by others to contribute to differences in mortality between settings with higher and lower infectious-disease burden, this hypothesis is not yet supported by epidemiological evidence.[27,28] In Zambia, systematic SARS-CoV-2 testing among general samples of decedents revealed prevalent unascertained infection,[5] and analyses of all-cause mortality during the COVID-19 pandemic have revealed under-reporting in other settings.[29] Similar assessments face difficulties in India, where vital registration systems may not capture or

assign accurate causes for many deaths. Prospective studies addressing mortality and its causes during the COVID-19 pandemic in India[30] are warranted to more clearly resolve the burden of disease in this setting.

Contributors

BW and JAL did the literature search. RL, CMB, VTG, KVAK, and JAL designed the study. CMB, VTG, and KVAK collected the data. JAL did the data analysis. The data were interpreted by all authors. JAL wrote the original draft of the manuscript, which was then reviewed and edited by all authors. JAL and CMB accessed and verified the data. All authors had full access to all the data. JAL had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

For more on **Tamil Nadu COVID-19 surveillance data** see https://tn.data.gov.in/

Aggregated facility-level and district-level COVID-19 surveillance data from Tamil Nadu are made available from their website. Individual-level testing and clinical outcomes data reported in this study are not publicly shared. Individuals wishing to access disaggregated data, including data reported in this study, should submit requests for access to CMB (ChandraMohanIAS@gmail.com). Deidentified data (including, as applicable, participant data and relevant data dictionaries) will be shared upon approval of analysis proposals with signed data-access agreements in place.

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