

**Total patient load, regional disparities and in-hospital mortality of intubated COVID-19 patients
in Greece, September 2020 to May 2021**

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Abstract

Aims: While healthcare services have been expanding capacity during the COVID-19 pandemic, quality of care under increasing patient loads has received less attention. We examined in-hospital mortality of intubated COVID-19 patients in Greece, in relation to total intubated patient load, Intensive Care Unit (ICU) availability and hospital region.

Methods: Anonymized surveillance data were analyzed from all intubated COVID-19 patients in Greece between 1 September 2020 and 6 May 2021. Poisson regression was used to estimate the hazard of dying as a function of fixed and time-varying covariates.

Results: Mortality was significantly increased above 400 patients, with an adjusted Hazard Ratio of 1.25, 95%CI: 1.03-1.51), rising progressively up to 1.57 (95%CI: 1.22-2.02) for 800+ patients. Hospitalization outside an ICU or away from the capital region of Attica were also independently associated with significantly increased mortality.

Conclusions: Our results indicate that in-hospital mortality of severely ill COVID-19 patients is adversely affected by high patient load even without exceeding capacity, as well as by regional disparities. This highlights the need for more substantial strengthening of healthcare services, focusing on equity and quality of care besides just expanding capacity.

Keywords (MeSH)

COVID-19; pandemic; healthcare disparities; intensive care units; right to health; quality of care; intubation; mortality

Word count

1,320 (full text), 185 (abstract)

Introduction

During the COVID-19 pandemic, healthcare systems' capacity and resilience has been in the spotlight [1]. However, less attention has focused on how the actual stress placed on healthcare services by COVID-19 has affected their performance [2, 3]. Even without exceeding nominal capacity, a high patient load could plausibly compromise quality of care, especially if occurring in a context of chronic underfunding or poor pandemic preparedness [4, 5].

In this context, the aim of our study was to examine how in-hospital mortality of intubated COVID-19 patients in Greece is affected by patient load, intensive care unit (ICU) availability and regional disparities.

Methods

In Greece the National Public Health Organization (NPHO) is responsible for COVID-19 surveillance, and does active case finding and follow-up of all laboratory-confirmed COVID-19 cases in the country that are intubated or hospitalized in an ICU. We obtained from NPHO anonymized patient data for all intubated cases from 1 September 2020 to 6 May 2021, including dates of intubation, extubation, ICU admission and discharge. As the study used only anonymous surveillance data from which no patient can be identified, no ethical approval was necessary. The analyzed data and analysis code are available online in the journal website.

For all cases follow-up time from intubation until extubation or death was split finely into days, and Poisson regression was used to estimate the hazard of dying (fatality rate per day of hospitalization) as a function of fixed and time-varying covariates [6]. To avoid bias, deaths occurring up to five days after extubation were classified as deaths at the end of follow-up. The current total of intubated COVID-19 patients at each time point during follow-up was used as an indicator of healthcare system stress, and was included as a time-varying categorical variable in the model (reference: 0-199 patients, vs 200-299, 300-399 etc up to 800+ patients). Age was modelled with a natural cubic spline with 1 internal knot. Other covariates included sex, a linear time trend, ICU hospitalization (vs non-ICU, for

each day of follow-up) and hospital region (the metropolitan regions of Attica and Thessaloniki, vs the rest of Greece, Supplementary Figure S1). Model-based effect estimates (Hazard Ratios) were also used to calculate Population Attributable Fractions [7]. Furthermore, we examined how the age distribution of patients varied in relation to patient load, region and ICU hospitalization, in order to better interpret the findings. All analyses were done in the R software environment version 4.0.4 [8].

Results

During the study period, two epidemic waves were observed in Greece; the first peaked in November 2020 and was focused in Central and Northern Greece, whereas the second was associated with the B.1.1.7 variant and affected Athens and the entire country. The series of new intubations, deaths among the study population, and total intubated COVID-19 patients are illustrated in Figure 1.

After excluding 296 cases with incomplete covariate information, 6282 cases were analyzed (Table 1) of whom 3988 died (63.5%). Most patients spent part or all of their hospital stay in an ICU (5971/6282, with 93951/97601 person-days total). Among those not admitted to an ICU, 275 (88.4%) died compared to 3713 (62.2%) among those admitted ($p < 0.001$).

Model results, expressed as adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI), are shown in Figure 2. There was a significant association between mortality and total intubated patients above 400, with its magnitude increasing progressively: from 1.25 (95%CI: 1.03–1.51) for 400–499 patients, up to 1.57 (95%CI: 1.22–2.02) for 800+ patients. Being intubated outside an ICU was strongly associated with mortality (HR 1.87, 95%CI: 1.65–2.12), as was age, particularly after 60 years old. Interestingly, being hospitalized outside the capital region of Attica was also associated with increased in-hospital mortality, with HRs of 1.35 (95%CI: 1.24–1.47) for Thessaloniki and 1.40 (95%CI: 1.30–1.51) for the rest of the country. There was no association with sex, but there was a small negative time trend (HR 0.97 per month, 95%CI 0.94–1.00, $p = 0.02$) indicating gradually lower mortality as the pandemic progressed.

Given the above associations, out of 3988 deaths reported, 947 (95%CI: 343–1460) were attributable

to the high load (≥ 200) of intubated COVID-19 patients, 133 (95%CI: 101–169) to being outside an ICU, and 656 (95%CI: 526–790) to being hospitalized away from Attica. A combined total of 1535 deaths (95%CI: 1053–1947) was attributable to these three factors collectively.

There was no association between patient age and total patients intubated, offering no evidence of patient selection with higher patient loads (Supplementary Figure S2). In contrast, patients who never entered an ICU were older on average (median 73 vs 68 years, $p < 0.001$). Also, patients hospitalized in Thessaloniki were slightly younger than those in Attica and other regions (median 67 vs 69 years, $p < 0.001$).

Discussion

Our analysis provides national-level evidence that in-hospital mortality of severely ill COVID-19 patients is adversely affected by high patient load. Importantly, this occurs not only when healthcare capacity is stressed to depletion, but also at intermediate stress levels, when the availability of resources and care is not nominally restricted. This represents a major preventable factor to limit avoidable deaths from COVID-19, and highlights the need for more extensive investment in healthcare beyond the minimum to meet peak demand during the pandemic, thereby ensuring adequate quality of care. Similar findings for COVID-19 patients have been recently reported from Veterans Affairs hospitals in the United States [2], and a large referral hospital in Northern Italy [3].

Our study further demonstrated important regional disparities, as in-hospital mortality was substantially lower for people hospitalized in Attica compared to the rest of the country. This highlights the chronically uneven regional distribution of healthcare resources in Greece, with beds, equipment and trained healthcare workers concentrated in metropolitan areas [9] (Supplementary Figure S1). It also compounds other existing health inequities that define the rural-urban divide, resulting in a higher COVID-19 case fatality ratio in underserved and rural areas despite higher exposure and mortality in cities [10, 11].

Our results must be interpreted with caution; as this is an observational study, there is a possibility that

patient selection (prioritizing for care those most in need and with a worse prognosis) might have influenced our associations. However, the lack of association between total patient load and the age of newly intubated patients suggests that those needing care did indeed receive it. In addition, patients in Thessaloniki were younger than those in Attica, thus residual confounding by age cannot explain their increased mortality. In contrast, patients treated outside an ICU were slightly older, thus some of them might have been deemed “too ill to benefit” from the ICU. A clear limitation of our analysis is the lack of information on comorbidities and baseline health status (at presentation to the hospital). However, both these factors are unlikely to be distributed differently over time, and are both correlated with and eclipsed by age, which is the major determinant of the risk of death and which we carefully adjusted for [12, 13]. Therefore the observed associations most likely reflect real and avoidable differences in the quality of care for COVID-19 patients, due to increased patient load, ICU availability and regional disparities. The precise mechanisms by which patient load is associated with increased mortality need to be investigated in future research, to allow for targeted interventions.

Nevertheless, these findings already highlight the need for strengthening healthcare systems in the context of pandemic preparedness, as scaling up capacity during a pandemic is constrained by factors such as the availability of trained healthcare staff. In Greece the increased healthcare worker needs due to COVID-19 were largely met with staff redeployments, short-term hirings, and requisitioning of private practitioners’ services [14, 15]. These might have been insufficient to counter the chronic underfunding and understaffing of public healthcare services as a consequence of the long economic crisis [16]. It is therefore essential to make long-term investments in health also for the post-COVID era, ensuring equitable access to high-quality care for all [17].

Acknowledgements

We acknowledge the staff of the National Public Health Organization for their hard work in coordinating the surveillance of COVID-19 in Greece.

Author contributions

Original idea: ST; Data analysis: TL; Data interpretation: TL, ST; First draft of the manuscript: TL;

Revision of the manuscript for important intellectual content: TL, ST

Conflicts of Interest

None. ST is an advisor to the Greek Ministry of Health; views expressed here are his own.

Funding

No funding was received for this study

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Table 1: Characteristics of the study population; laboratory-confirmed COVID-19 cases in Greece intubated between 1 September 2020 and 6 May 2021

	Total	Survived	Died	p-value*
Number of patients	6282	2294	3988	
Median age, years (IQR)	68 (60–75)	63 (54–71)	71 (63–77)	<0.001
Sex				0.53
Female	2191 (100)	812 (37)	1379 (63)	
Male	4091 (100)	1482 (36)	2609 (64)	
Hospitalization type				<0.001
In the ICU	5971 (100)	2258 (38)	3713 (62)	
Outside the ICU	311 (100)	36 (12)	275 (88)	
Hospital region				<0.001
Attica	2811 (100)	1199 (43)	1612 (57)	
Thessaloniki	1492 (100)	511 (34)	981 (66)	
Rest of Greece	1979 (100)	584 (30)	1395 (70)	
Total number of people intubated (at date of intubation)				<0.001
0-199	496 (100)	172 (35)	324 (65)	
200-299	514 (100)	186 (36)	328 (64)	
300-399	678 (100)	215 (32)	463 (68)	
400-499	831 (100)	256 (31)	575 (69)	
500-599	1007 (100)	258 (26)	749 (74)	
600-699	805 (100)	242 (30)	563 (70)	
700-799	1021 (100)	419 (41)	602 (59)	
800+	930 (100)	546 (59)	384 (41)	

* Mann-Whitney test for continuous variables, Fisher's test for categorical variables

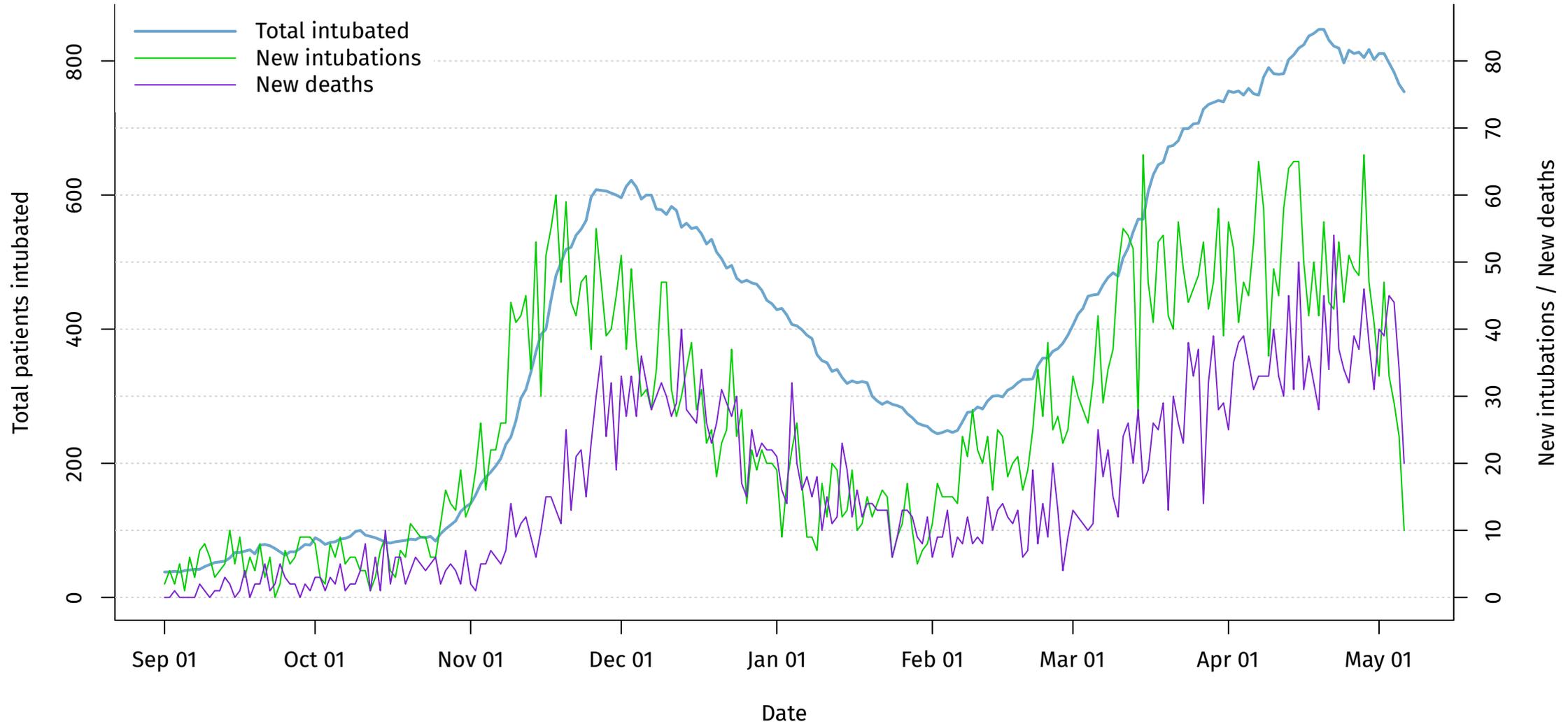
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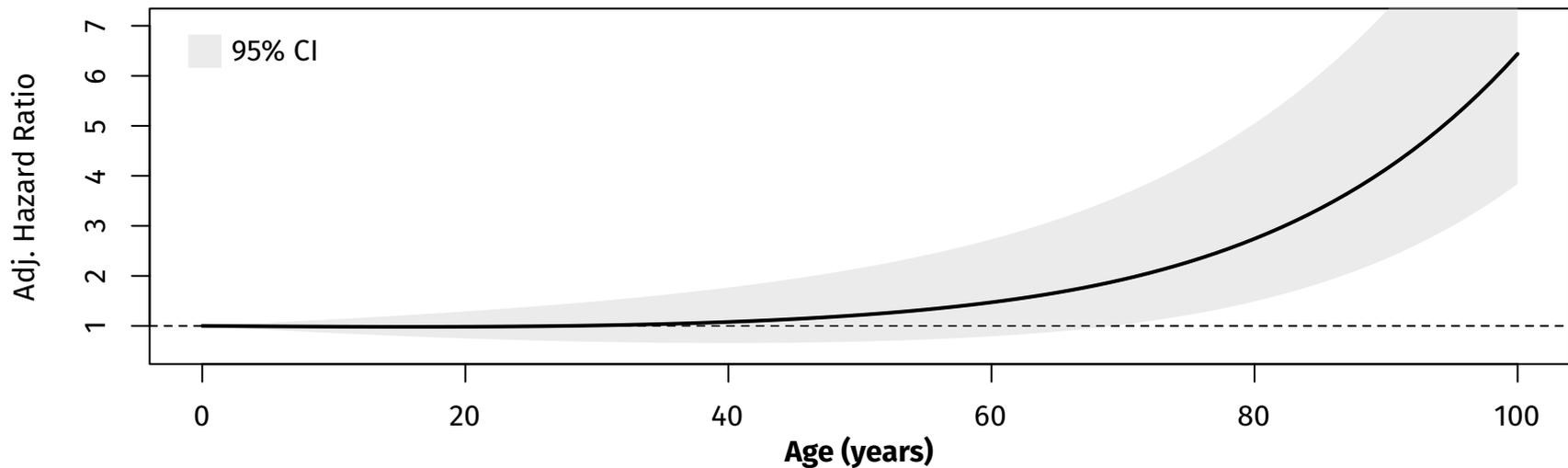
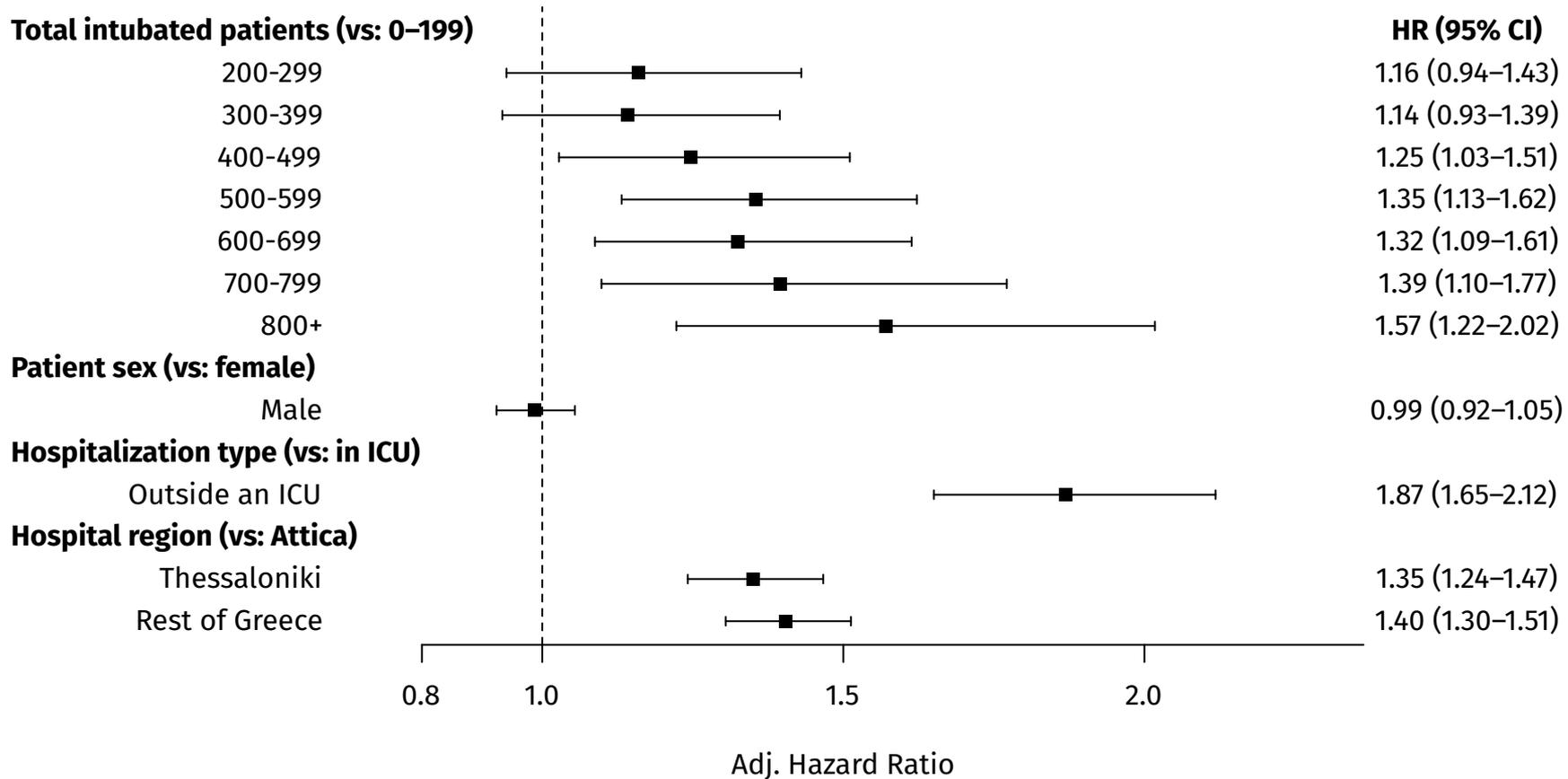
Figure 1: Distribution over time of total intubated COVID-19 patients, new intubations and deaths among the study population, Greece, 1 September 2020 to 6 May 2021.

Figure 2: Multivariable (adjusted) associations between in-hospital mortality of intubated COVID-19 patients and age, sex, hospitalization type, hospital region and patient load, Greece, 1 September 2020 to 6 May 2021.

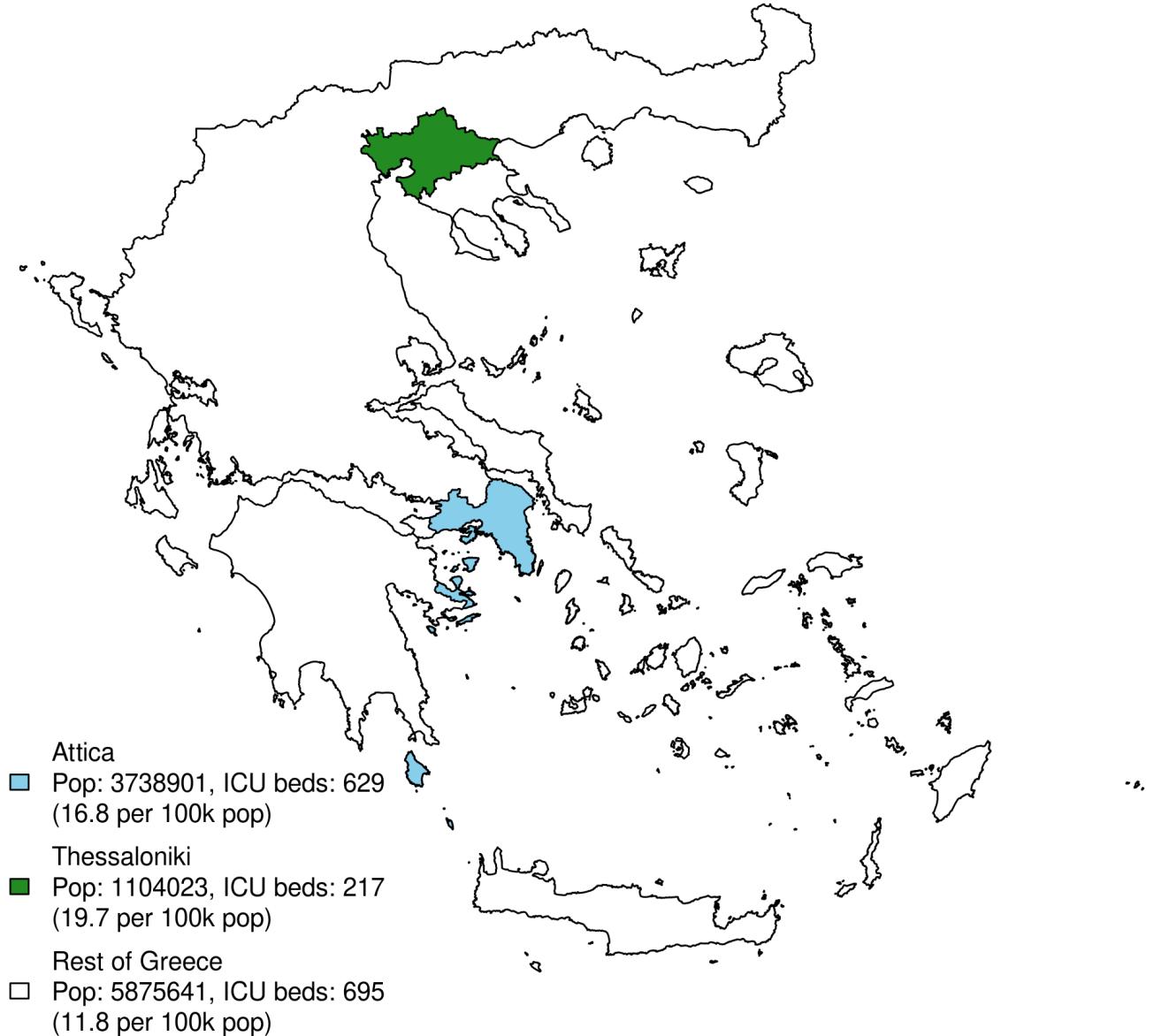
Supplementary Figure 1: Study regions in Greece and distribution of ICU beds, as of 20 April 2021

Supplementary Figure 2: Patient age distribution in relation to patient load, hospitalization type (inside/outside ICU) and hospital region, Greece, 1 September 2020 to 6 May 2021.

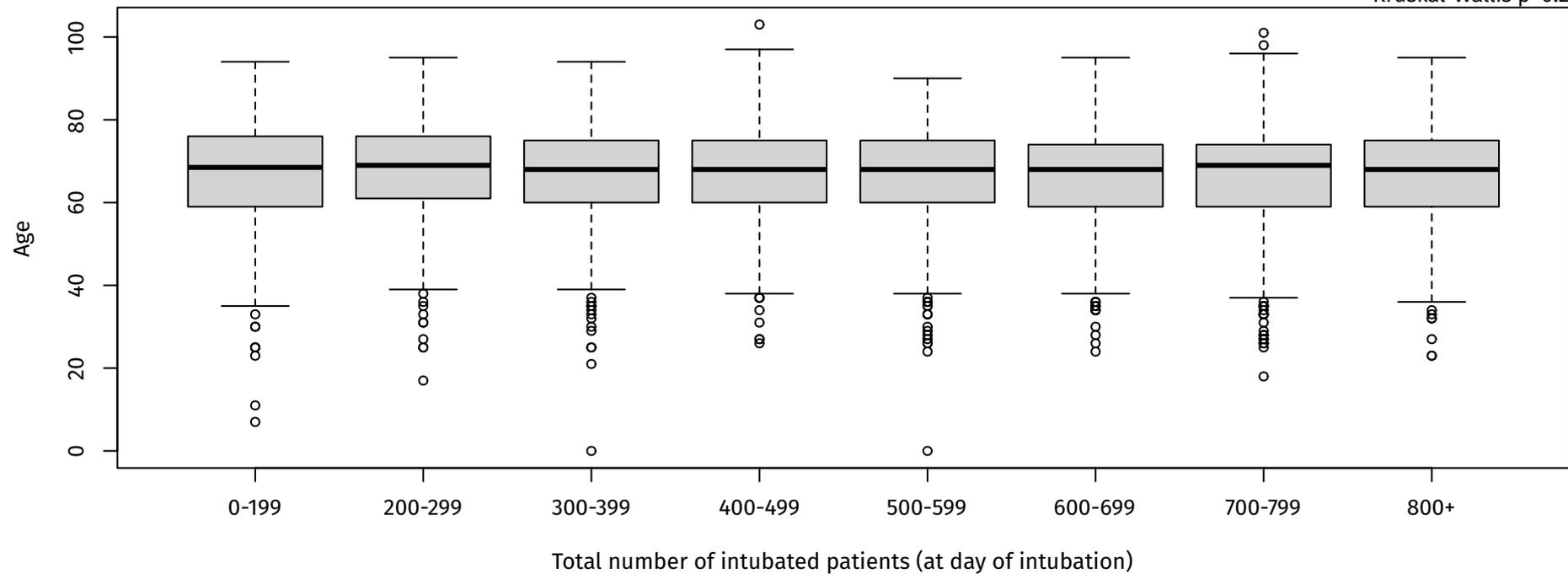




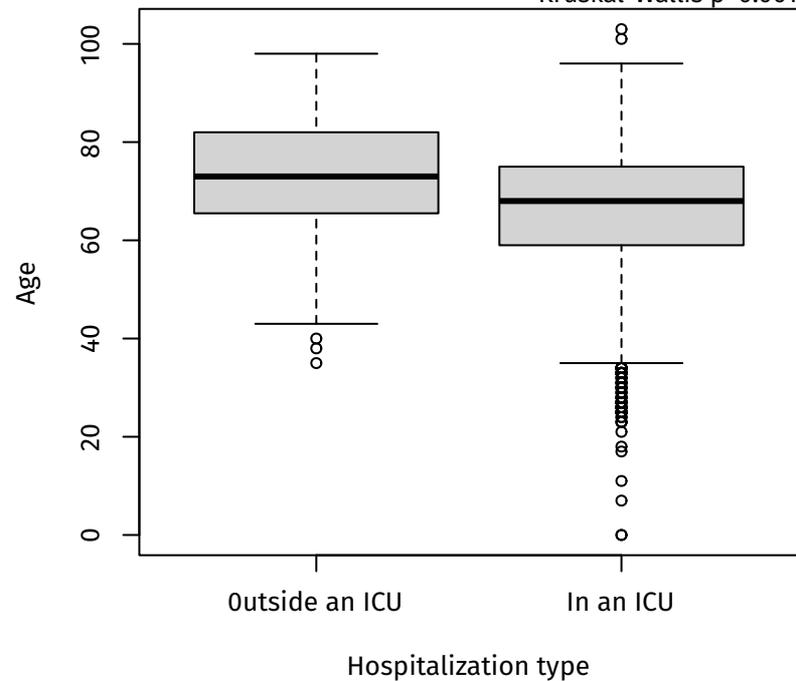
Total ICU beds in Greece, as of 20 April 2021



Kruskal-Wallis p=0.2



Kruskal-Wallis p<0.001



Kruskal-Wallis p<0.001

