

23 **Abstract**

24 **Background** The management of healthcare workers (HCWs) exposed to confirmed cases of
25 COVID-19 is still a matter of debate. It is unclear whether these subjects should be tested in
26 the absence of symptoms and if those can guide diagnosis.

27 **Methods** Occupational and clinical characteristics of all the consecutive HCWs who
28 performed a nasopharyngeal swab for the detection of SARS-CoV-2 in a University Hospital
29 from February 24, 2020, to March 31, 2020, were collected. Frequencies of positive tests
30 were compared according to selected variables. Multivariable logistic regression analyses
31 were then applied.

32 **Findings** Positive tests were 138 among 1,573 HCWs (8.8%, 95% confidence interval [CI]:
33 7.4-10.3), with a marked difference between symptomatic (20.2%, 95% CI: 16.7-24.1) and
34 asymptomatic (3.7%, 95% CI: 2.7-5.1) subjects ($p < 0.001$). Physicians were the group with
35 the highest frequency of positive tests (10.6%, 95% CI: 8.3-13.4) whereas clerical workers
36 and technicians displayed the lowest frequency (2.9%, 95% CI: 0.8-7.3). The likelihood of
37 being positive increased with the number of reported symptoms and the strongest predictors
38 of a positive test were taste and smell alterations (odds ratio [OR]= 29.7) and fever (OR =
39 7.21). The median time from first positive test to a negative test was 23 days (95% CI: 19-
40 24).

41 **Interpretation** In this Italian group of HCWs exposed to confirmed cases of COVID-19 the
42 presence of symptoms, especially taste and smell alterations and fever, was associated with
43 SARS-CoV-2 infection. The median time to clear the virus from nasopharynx was 23 days.

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45 **Research in context**

46 **Evidence before this study** We searched PubMed for articles published in English up to
47 April 25, 2020, using the keywords “SARS-CoV-2”, “COVID-19”, “2019-nCoV”, AND
48 “healthcare workers”, “HCW”, AND “testing”, “nasopharyngeal swab”. We found one
49 article: *Roll-out of SARS-CoV-2 testing for healthcare workers at a large NHS Foundation*
50 *Trust in the United Kingdom, March 2020* published in *Euro Surveillance*. Reviewing the
51 pre-print website medRxiv with the same keywords we identified two additional studies:
52 *SARS-CoV-2 infection in Health Care Workers in a large public hospital in Madrid, Spain,*
53 *during March 2020,* and *SARS-CoV-2 infection in 86 healthcare workers in two Dutch*
54 *hospitals in March.*

55 **Added value of this study** We showed that, even if symptomatic healthcare workers had a
56 much higher probability of positive test, almost one third of those infected were
57 asymptomatic. Specific symptoms, namely taste and smell alterations and fever, were
58 strongly associated with the infection. Finally, the median time to clear the virus from
59 nasopharynx was 23 days.

60 **Implications of all the available evidence** Screening strategies for healthcare workers
61 exposed to COVID-19 patients should take in account the significant proportion of
62 asymptomatic carriers and the predictive role of specific symptoms. Moreover, healthcare
63 workers coming back to work after a positive test should be aware of the long-time of viral
64 shedding from nasopharynx.

65 **Introduction**

66 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown
67 virus which recently jumped from a not yet identified animal host to humans and it is
68 responsible of coronavirus disease 2019 (COVID-19).¹ This disease is characterized by a
69 wide array of manifestations, ranging from an asymptomatic infection to a severe respiratory
70 insufficiency requiring mechanical ventilatory support.² The virus has now spread worldwide
71 from China, causing the first pandemic of the XXI century, disrupting health-care services in
72 the affected countries and exacting a terrific toll of human lives.³⁻⁴ A critical element of the
73 virus is its basic reproduction number (R_0) ranging from 2.76 to 3.28.^{5,6} This is the
74 consequence of specific viral properties, the large number of asymptomatic, and thus
75 undetected, carriers and the long duration of viral detectability, even after clinical cure.⁷⁻¹⁰
76 Currently, the only available method to ascertain the presence of SARS-CoV-2 infection is
77 the detection of unique sequences of virus RNA by real-time reverse-transcription
78 polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when
79 necessary.¹⁰

80 Healthcare workers (HCWs) are a crucial actor of this pandemic with a Janus role. Indeed,
81 they are acting in an emergency situation to mitigate the effects of the pandemic, but
82 consequently they are continuously at risk of being infected. At the same time, they are in
83 contact with the most fragile elements of our society, those who need health assistance. It is
84 therefore mandatory to avoid that infected HCWs act as spreaders of the disease.

85 Unfortunately, it is still unclear which microbiologic investigations and procedures should be
86 adopted toward HCWs in COVID-19 settings, especially to those exposed to confirmed cases
87 of COVID-19 and at risk for infection. To answer this question, we reviewed all the
88 nasopharyngeal swab performed in HCWs exposed to confirmed cases of COVID-19 at the
89 Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico located in Milan, the capital

90 of Lombardy, by large the Italian region mostly affected by COVID-19.¹¹ We assessed
91 frequency of positive tests among symptomatic and asymptomatic subjects and evaluated the
92 association between occupation, symptoms (type and number), and presence of the infection.
93 Furthermore, we also calculated the median time between the day of diagnosis (first positive
94 test) and the day in which the HCW became test-negative.

95 **Materials and methods**

96 We collected occupational and clinical characteristics of all the consecutive HCWs who
97 performed a nasopharyngeal swab for the detection of SARS-CoV-2 at the Foundation
98 IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy in the period from
99 February 24, 2020, (the day after the first COVID-19 case occurred in a physician of our
100 hospital) to March 31, 2020. For these workers, we collected laboratory results as of April 9,
101 2020. We tested HCWs at risk for infection, which is defined as a contact with a patient or
102 another HCW with (or later diagnosed with) SARS-CoV-2 infection. HCWs were subdivided
103 into physicians (including residents), nurses and midwives, healthcare assistants, health
104 technicians, and clerical workers and technicians. All the information was collected by the
105 infectious disease notification form associated to each test. Subjects were defined as
106 symptomatic if presented any of the following in the 14 days preceding the test: fever, cough,
107 dyspnoea, asthenia, myalgia, coryza, sore throat, headache, ageusia or dysgeusia, anosmia or
108 parosmia, ocular symptoms, diarrhoea, nausea, and vomit. The study was approved by the
109 Ethical Committee of our institution and was conducted in accordance with the Helsinki
110 Declaration.

111 *SARS-CoV-2 detection*

112 For viral detection two different methods were used. The first one employed Seegene Inc
113 reagents (Seoul, Korea). RNA extraction was performed with STARMag Universal Cartridge

114 kit on Nimbus instrument (Hamilton, Agrate Brianza, Italy) and amplification with Allplex®
115 2019-nCoV assay. The second one employed a GeneFinder® COVID-19 Plus RealAmp Kit
116 (OSANG Healthcare, Anyangcheondong-ro, Dongan-gu, Anyang-si, Gyeonggi-do, Korea) on
117 ELITech InGenius® instrument (Torino, Italy). Both assays identify the virus by multiplex
118 rRT-PCR targeting three viral genes (E, RdRP and N).

119 *Statistical analysis*

120 We compared frequencies of positive tests according to selected variables using chi-squared
121 test, adjusted odds ratios (OR), and 95% confidence intervals (CI) calculated with a
122 multivariable logistic regression model including as covariates gender, age class, occupation,
123 and having reported any symptom. We evaluated the discriminating ability of the number of
124 reported symptoms in a univariate logistic model and assessed the performance of each of 11
125 groups of symptoms by fitting a multivariable logistic model containing all groups of
126 symptoms. Area under the ROC curve (AUC) was calculated after these models. We
127 calculated the time since first positive test until subjects became negative by using the
128 Kaplan-Meier function. Log-rank test was used to evaluate the association of gender, age
129 class, or symptoms with median time to test negativity. Statistical analysis was performed
130 with Stata 16 (StataCorp. 2019)

131 **Results**

132 In the period from February 24, 2020, to March 31, 2020, 1,573 HCWs, 1,010 women
133 (64.2%) and 563 men (35.8%) performed at least a first nasopharyngeal swab for the
134 detection of SARS-CoV-2. Mean age was 44.5 years and the majority (about 70%) were
135 physicians (including residents) or nurses/midwives (table 1). One third of women and one
136 fourth of men reported having had at least one symptom at the time of testing. The majority
137 (73.9%) performed only one test, while 411 individuals (26.1%) had from two to six tests.

138 The overall frequency of subjects with at least one positive test was 8.8% (95% CI: 7.4-
139 10.3%) (table 2). The frequency of positive tests ranged from 8.0% (healthcare assistants) to
140 10.6% (physicians), much higher than among clerical workers (2.9%). Among subjects with
141 symptoms the frequency of positive tests was 20.2%, while among asymptomatic HCWs the
142 frequency was much lower (3.7%). However, among the 138 HCWs with positive test,
143 41/138 (29.7%) were asymptomatic. The predictive role of occupation and presence of
144 symptoms was confirmed in the multivariable logistic model.

145 The likelihood of being positive increased with the number of reported symptoms (table 3).
146 All symptoms excluding sore throat were positively associated with test positivity, especially
147 fever and taste and smell alterations (table 4). In a multivariable model, the strongest
148 predictors of a positive test were taste and smell alterations (OR = 29.7) and fever (OR =
149 7.21), followed by myalgias, asthenia, ocular symptoms, and dyspnoea (ORs ranging from
150 1.98 and 2.77). The AUC from the model including these six group of symptoms was 0.74
151 (95% CI: 0.70-0.79), similar to an AUC of 0.77 (95% CI: 0.72-0.81) when including all
152 symptoms. Sore throat was negatively associated with positivity (OR = 0.35).

153 Among the 138 positive HCWs, 99 (71.7%) were already positive at first testing, while 39
154 (28.3%) were found positive in a subsequent test. At the time of last test performed, 69/138
155 (50.0%) were still positive. The median time from first positive test to a negative test was 23
156 days (95% CI: 19-24) (figure 1). However, 9/69 subjects (13.0%) were still positive 24 to 31
157 days since first positive test. Median time was identical in subjects with symptoms (23 days,
158 95% CI: 18-26) and in those without symptoms (23 days, 95% CI: 19-29). Median time was
159 also not associated with gender ($p=0.84$) nor age ($p=0.83$). As of March 31, 2020, five
160 workers, four men (three physicians and a nurse) and a woman (clerical worker) were
161 hospitalized.

162 A minority of the HCWs (81/1,537, 5.3%) reported to have had a contact with an infected
163 person outside the hospital (relatives, colleague, or friends). Of these, 12 (8.7%) were found
164 to be positive.

165 **Discussion**

166 In this Italian group of HCWs exposed to confirmed cases of COVID-19, the presence of
167 symptoms, and particularly taste and smell alterations and fever, was associated with
168 positivity of nasopharyngeal swab for SARS-CoV-2. Despite the low relative frequency of
169 positive tests among asymptomatic subjects, their number was high in absolute terms (just
170 about one third of all infected subjects). Interestingly, the AUC of a model considering six
171 groups of symptoms (fever, myalgia, asthenia, ocular symptoms, dyspnoea, and taste and
172 smell alterations) was 0.74. Based on these results, it seems reasonable to tailor the screening
173 approach of HCWs at risk based on the resources available. In low-resource settings we
174 suggest focusing to test those with symptoms to maximize efficacy, especially considering
175 the continuous exposure of HCWs to at risk situations, thus requiring repeated testing
176 sessions. Nevertheless, it should be underlined that in our study 41/138 subjects (29.7%) were
177 infected but displayed no symptoms, meaning that one third of those infected can be lost with
178 a symptoms-based screening strategy. Therefore, in middle- and high-resource settings a
179 mass screening for all HCWs exposed to confirmed COVID-19 cases appears the best
180 approach to limit the spread of the virus. More detailed cost-effectiveness study,
181 encompassing the epidemiological context, should be performed to define the optimal
182 method.

183 The frequency of positive subjects among symptomatic workers in our study population
184 (20.2%) is similar to the one (18%) reported by Keeley and colleagues¹² in their cohort
185 composed of 1,533 symptomatic HCWs presenting with fever plus one among cough, sore

186 throat, runny nose, myalgia, headache and persistent cough. However, it should be remarked
187 that focussing only on symptomatic workers results in missing a significant number of
188 infected subjects. Indeed, we had 67/138 (48.5%) positive HCWs presenting without or with
189 only one symptom. When we consider the overall frequency, our proportion of positive
190 subjects (8.8%) is comparable to the 6% described by Kluytmans-van den Bergh et al. in a
191 small Dutch cohort of HCWs, whereas it is significantly lower than the 38% reported by
192 Folgueira and colleagues in their Spanish cohort.^{13,14}

193 When stratified according to occupation, test-positive frequencies were clearly higher among
194 subsets with direct contact with patients (physicians including residents, nurses and
195 midwives, healthcare assistants and health technicians) than those without (clerical works and
196 technicians). Consequently, careful screening of these groups of workers should be
197 mandatory. No differences in terms of infection prevalence were seen between different age
198 groups nor between men and women, suggesting that risk factors for acquiring COVID-19
199 among HCWs are unrelated to age and sex.

200 Another relevant point is the significant number of subjects who were negative at the first test
201 but resulted positive when tested a second time. This might represent a serious concern, as a
202 discrete fraction of those can further spread the virus unnoticed, thus hampering the efficacy
203 of the screening strategy. It should be noted, however, that the second test was performed on
204 a small number of operators and not on a routine basis, making these considerations subject
205 to several potential biases. In addition, in a relevant proportion of our population we could
206 not retrieve information about the most likely date of exposure to a documented COVID-19
207 case. Thus, we cannot exclude a recent contact in which case the first test may have been
208 performed too early (i.e. still in the incubation period which has been estimated to be five
209 days), before a sufficient amount of viral particles is detectable in the nasopharynx.¹⁵

210 Moreover, it has to be considered that HCWs employed in COVID-19 units/hospitals are at

211 risk of SARS-CoV-2 exposure on a daily basis and therefore repeated exposures, even
212 unnoticed, can occur also after the first one who motivated the test. Moreover, technical
213 limitation can be responsible of falsely negative test, considering that the sensitivity of
214 nasopharyngeal swab for SARS-CoV-2 detection has been estimated to be around 71%.¹⁶

215 Finally, even if it was not the main goal of our study (because a longer follow-up time would
216 be required), we observed a median time from first positive test to a negative test of 23 days.
217 This is in accordance with several already published reports and have a significant impact on
218 the efficiency of health systems.¹⁷⁻¹⁹ Indeed, it means that an infected HCW will be
219 unavailable to perform its duty for at least three weeks since diagnosis (or even four weeks if
220 we consider the upper 95% confidence limit). Our results were based on a three genes
221 qualitative RT-PCR. To understand the real significance of this viral detection new studies
222 assessing the infectivity of viral particles and the possible impact of quantitative techniques
223 are needed.

224 In conclusion, our results show that symptomatic HCWs exposed to confirmed cases of
225 COVID-19 are almost eight times more likely to be infected than asymptomatic HCWs.
226 Nevertheless, also a non-negligible amount of asymptomatic HCWs is infected and accounts
227 for almost one third of positive tests. Therefore, screening strategies may be tailored
228 according to the available resources. Taste and smell alterations and fever should be
229 considered the most relevant alarm bells suggesting the opportunity of performing a test.

230 Finally, the median time to become non-infective exceeded three weeks. Consequently, the
231 suggested quarantine period of 14 days after exposure to a confirmed case should be revised.
232 The correct length of this period as well as the best moment to perform a nasopharyngeal
233 swab (measured in days after exposure) have to to be determined.

234 **Authors contributions** AL, DC and AG conceived the study. APC, BT, VC, EP and LR
235 collected the data. DC, MC, and ACP performed statistical analyses. AL and DC wrote the
236 first draft. All co-authors revised the manuscript.

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242 **Conflict of interests:** none related to the content of this manuscript.

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288

289 **Figures/tables**

290 **Table 1.** Characteristics of 1,573 healthcare workers tested for SARS-CoV-2 in Milan, Italy,
 291 in the period from February 24, 2020, to March 31, 2020.

Variable	Women		Men		Total	
	N	%	N	%	N	%
All subjects	1010	100	563	100	1573	100
Age (years), mean (min-max)	44.2	(21-67)	45.1	(22-76)	44.5	(21-76)
Age (years)						
<30	152	15.1	96	17.0	248	15.8
30-39	255	25.2	132	23.5	387	24.6
40-49	217	21.5	109	19.4	326	20.7
50-59	314	31.1	130	23.1	444	28.2
60+	72	7.1	96	17.0	168	10.7
Occupation						
Physicians, including residents	295	29.2	287	51.0	582	37
Nurses, midwives	388	38.4	134	23.8	522	33.2
Healthcare assistants	122	12.1	40	7.1	162	10.3
Health technicians*	133	13.2	37	6.6	170	10.8
Clerical workers, technicians	72	7.1	65	11.5	137	8.7
At least one symptom	343	34.0	137	24.3	480	30.5
No. tests performed						
1	759	75.1	403	71.6	1162	73.9
2	161	15.9	99	17.6	260	16.5
3	59	5.8	40	7.1	99	6.3
4	19	1.9	12	2.1	31	2.0
5	9	0.9	3	0.5	12	0.8
6	3	0.3	6	1.1	9	0.6

292

293 *Includes biologists, radiology and laboratory technicians, psychologists, other health
 294 technicians

295

296 **Table 2.** Association between selected variables and frequency of at least one positive test
 297 among 1,573 healthcare workers tested for SARS-CoV-2 in Milan, Italy, in the period from
 298 February 24, 2020, to March 31, 2020.

	Subjects	Positive test				
	N	N	%	p-value*	OR**	95% CI**
All	1573	138	8.8	7.4-10.3
Women	1010	83	8.2	0.30	1.00	Reference
Men	563	55	9.8	..	1.41	0.95-2.10
Age (years)						
<30	248	29	11.7	0.50	1.00	Reference
30-39	387	34	8.8	..	0.76	0.44-1.33
40-49	326	26	8.0	..	0.66	0.37-1.20
50-59	444	35	7.9	..	0.71	0.40-1.26
60+	168	14	8.3	..	0.69	0.34-1.41
Occupation						
Physicians, including residents	582	62	10.6	0.07	4.95	1.72-14.3
Nurses, midwives	522	43	8.2	..	3.11	1.07-9.04
Healthcare assistants	162	13	8.0	..	2.98	0.92-9.62
Health technicians	170	16	9.4	..	3.33	1.06-10.5
Clerical workers, technicians	137	4	2.9	..	1.00	Reference
Any symptom						
No	1093	41	3.7	<0.001	1.00	Reference
Yes	480	97	20.2	..	7.55	5.07-11.2

299
 300 Abbreviations: CI, confidence interval; OR, odds ratio.
 301 *From chi-squared test.
 302 **From a multivariable logistic model including gender, age class, occupation, and any
 303 symptom.
 304

305 **Table 3.** Association between number of symptoms and frequency of at least one positive test
306 among 1,573 healthcare workers tested for SARS-CoV-2 in Milan, Italy, in the period from
307 February 24, 2020, to March 31, 2020.

	Subjects	Positive test				
	N	N	%	p-value*	OR**	95% CI**
Number of symptoms						
No symptoms	1093	41	3.7	<0.001	1.00	Reference
1	191	26	13.6	..	4.04	2.41-6.79
2	145	29	20.0	..	6.41	3.84-10.7
3	98	27	27.8	..	9.76	5.67-16.8
4	35	10	28.6	..	10.3	4.63-22.8
5	7	3	42.8	..	19.2	4.17-88.8
6	4	2	50.0	..	25.7	3.53-186

308
309 Abbreviations: CI, confidence interval; OR, odds ratio.
310 *From chi-squared test.
311 **From a univariate logistic model.

312

313 **Table 4.** Association between selected symptoms and frequency of at least one positive tests
 314 among 1,573 healthcare workers tested for SARS-CoV-2 in Milan, Italy, in the period from
 315 February 24, 2020, to March 31, 2020.

	Subjects	Positive test				
	N	N	%	p-value*	OR**	95% CI**
Specific symptom						
Cough						
No	1350	93	6.9	<0.001	1.00	Reference
Yes	223	45	20.2	..	1.32	0.80-2.16
Fever						
No	1382	74	5.4	<0.001	1.00	Reference
Yes	191	64	33.5	..	7.21	4.45-11.7
Sore throat						
No	1424	128	9.0	0.35	1.00	Reference
Yes	149	10	6.7	..	0.35	0.16-0.73
Coryza						
No	1465	115	7.8	<0.001	1.00	Reference
Yes	108	23	21.3	..	1.47	0.76-2.82
Headache						
No	1490	120	8.0	<0.001	1.00	Reference
Yes	83	18	21.7	..	0.69	0.34-1.39
Myalgias						
No	1517	122	8.0	<0.001	1.00	Reference
Yes	56	16	28.6	..	1.98	0.92-4.25
Diarrhoea/nausea/vomit						
No	1528	128	8.4	0.001	1.00	Reference
Yes	45	10	22.2	..	1.42	0.59-3.40
Asthenia						
No	1535	126	8.2	<0.001	1.00	Reference
Yes	38	12	31.6	..	2.03	0.87-4.75
Ocular symptoms						
No	1539	127	8.2	<0.001	1.00	Reference
Yes	34	11	32.3	..	2.77	1.07-7.18
Dyspnoea						
No	1548	131	8.5	0.001	1.00	Reference
Yes	25	7	28.0	..	2.07	0.74-5.79
Taste and smell alterations						
No	1551	122	7.9	<0.001	1.00	Reference
Yes	22	16	72.7	..	29.7	10.1-87.5

316

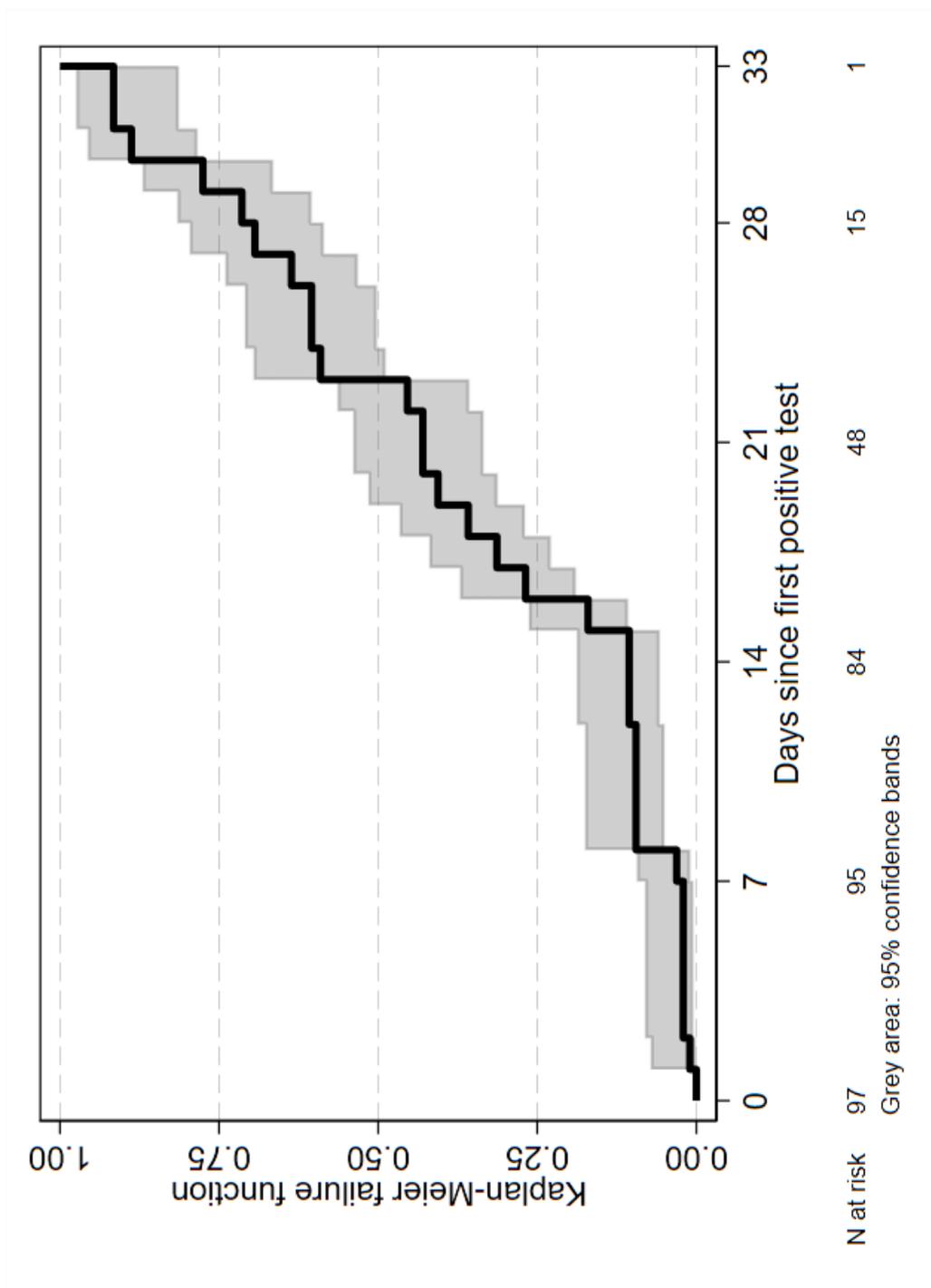
317 Abbreviations: CI, confidence interval; OR, odds ratio.

318 *From chi-squared test.

319 **From a multivariable logistic model including all symptoms.

320

321 **Figure 1.** Kaplan-Meier failure function showing times at which subjects became test-
322 negatives.



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