A Systematic Review and Provisional Meta-analysis on Psychopathologic Burden on Health Care Workers of Coronavirus Outbreaks

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Background: The new coronavirus (SARS-CoV-2) shows several similarities with previous outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Aim of this systematic review and meta-analysis is to provide evidence of the psychopathologic burden on health care workers (HCWs) of the first two deadly coronavirus outbreaks to get lessons for managing the current burden of COVID-19 outbreak.

Method: According to Cochrane Collaboration guidelines and the PRISMA Statement, the study quantified the effects of frontline work on mental health of HCWs. Major databases — Pubmed, Scopus, Embase, Medline, and Web of Science — were searched for observational and case-control studies evaluating mental health indexes reported by front-line work. This study computed the percentage of sample that reported clinically significant levels of psychiatric symptoms. Cohen’s d was used for comparing mental health outcomes of health care workers directly involved in addressing pandemic emergency with a control group that was not directly exposed to such conditions. Pooled effect sizes ($d_{w}$) were estimated whenever at least three independent studies yielded data. Heterogeneity of findings and bias of publication were estimated as well.

Findings: Fifteen studies have been selected for a total of 7,393 HCWs. From 9.6% to 51% of HCWs reported symptoms of Post-Traumatic Stress Disorder (PTSD) and from 20% to 75% reported psychiatric symptoms, with a prevalence of anxiety and depression. From one to the three years after outbreak, from 2% to 19% reported PTSD symptoms and from 5% to 90% psychiatric symptoms. Interestingly, HWCs who were directly involved in pandemic emergency showed significantly higher depressive and anxious
INTRODUCTION

Several viral diseases have emerged and impacted healthcare systems worldwide. Apart from the pure medical response, a major issue in dealing with viral pandemic is the human aspect.

The novel coronavirus infection (SARS-CoV-2) and related syndrome (COVID-19) was first identified in Wuhan, China, in December 2019 (1), with a declaration of pandemic on March 11, 2020 (2). Previous coronavirus outbreaks resulted in a major global public crisis. In November 2002, in China’s Guangdong, Severe Acute Respiratory Syndrome (SARS-CoV) was first detected. It lasted 80 days (from mid-March 2003 till 31 May 2003) when Singapore was removed from the World Health Organization (WHO) list of SARS (3). SARS was characterized by atypical pneumonia and droplet transmission.

The SARS outbreak had an important concentration in health care settings and a large number of health care workers who have been infected, with an estimate of more than 20% of those who contracted the disease (3). During the SARS outbreak, more than 8,000 individuals in 29 countries were infected over 7 months (4).

After the emergence of SARS, the Middle East Respiratory Syndrome (MERS-CoV) was the second coronavirus infection resulting in a major global public health crisis. It first emerged in 2012 in Saudi Arabia (5, 6), with an outbreak infection occurring in Korea from May to December 2015. The virus caused a total of 2,279 cases from 27 countries, till the end of February 2019 (7), with health care workers who continue to be at higher risk of being affected (1).

The COVID-19 showed several similarities with the SARS, and MERS, about the clinical presentations, which can vary from asymptomatic infection to severe or fatal disease and it is highly transmissible. The most common onset symptoms of the COVID-19 include fever, dry cough, muscle pains, lethargy and fatigue. However, the spread of COVID-19 infection is much broader than SARS or MERS and involves larger numbers of patients (8). From now, COVID-19 killed a higher number of people than MERS and SARS together, in spite of a fatality rate around 2%, compared to a case fatality rate of around 10% for SARS, with 34% of affected people killed by MERS between 2012 and 2019 (9).

All the physicians and nurses embedded in emergency care are under extreme psychological pressure and are at high risk of developing psychological diseases, with protracted working hours and unexpected changes in the sort of work (10). This situation may result in severe psychological distress and could lead to burnout (11). The analysis of the psychopathologic burden of previous outbreaks may help to understand the likely consequences for HCWs of the current pandemic of COVID-19, to plan psychological interventions and prevent future negative outcomes.

The objective of our study is to provide a systematic review of the psychological and psychopathological burden on HCWs of the two first deadly coronavirus outbreaks (SARS and MERS).

METHODS

The objective of this systematic review is to analyze all observational studies realized on the burden on mental health of caring for patients affected by MERS and SARS. The case-control study design, adequacy of sample size, comparison and outcome measures have been all carefully analyzed to guarantee the right inclusion of selected studies.

Search Strategy

Electronic searches were conducted on the major databases in the field of health and social sciences — Pubmed, Scopus, Embase, Medline, and Web of Science — in order to include the broadest range of relevant literature.

The selection of the search terms is based on the clinical experience and the topic literature on mental health (12). The search was performed using Mesh terms/Keywords (depending on the database) with the same search strategy: “Health Worker” AND “Epidemic” OR “MERS” OR “SARS” OR “Outbreak” AND “Depression” OR “Anxiety” OR “Burnout” OR “PTSD” OR “Suicide”. 
The search was limited to English-written publications, and to the period from 2002 to April 2020. When the full text was not retrievable, the study was excluded. Study selection was performed by independent reviewers with research expertise in clinical psychology who assessed the relevance of the study for the objectives of this review (Figure 1).

An additional analysis of the reference list was performed in each selected paper as well. When the full text was not retrievable, the study was excluded. It has been selected a final number of fifteen studies.

Inclusion Criteria:

- Studies should report data on mental health indexes linked to epidemic infections (SARS, MERS).
- Studies with an analytical study design as defined by Grimes and Schulz (13) (i.e., an observational study with a comparison or control group).
- Studies adopting standardized and validated instruments to assess psychological factors.
- Studies written in English.

Exclusion Criteria:

- Case reports, reviews, Letters to the Editor.
- Number of subjects per group ≤5.
- Qualitative studies.

Data Extraction

Study selection was performed by independent reviewers with research expertise in clinical psychology (FG, FM, RF) who assessed the relevance of the study for the objectives of this review. This first round of selection was based on the title, abstract, and keywords of each study. If the reviewers did not reach a consensus or the abstract did not contain sufficient information, the full text was reviewed.

In the second phase (screening), full-text reports have been evaluated to detect whether the studies met the inclusion criteria (Figure 1). In the phase of eligibility, full texts have been retrieved, and a final check was made to exclude papers not responding to inclusion/exclusion criteria, and reaching the final consensus to decide the final number of studies to be selected.

A standardized data extraction form was prepared; data was independently extracted by two of the authors (FG and RF) and inserted in a study database (Cohen’s $k = .85$) (14).

A process of discussion/consensus moderated by a third reviewer (GP) (15) resolved discrepancies between reviewers (for three studies).

**FIGURE 1** | PRISMA flow diagram of literature search and selection of publications.
Statistical Methods
A systematic analysis was conducted according to the Cochrane Collaboration guidelines (15) and the PRISMA Statement (16). The current review provided a quantitative approach for aggregating results of studies considering as the main outcomes the percentage of sample that reported clinically significant levels of overall and specific psychiatric symptoms (i.e., PTSD, depression and anxiety) (Figures 2–4) (for a description of cut-off scores see Table 1). Furthermore, this work aims at quantifying mental health consequences of the direct exposure to clinical management of pandemic emergency. Accordingly, meta-analytic procedures were conducted comparing levels of different mental health outcomes of health care workers directly involved in addressing pandemic emergency to a control group that was not directly exposed to such conditions. Cohen’s $d$ (32) was used as measure of effect size. Cohen’s $d$ was primarily calculated using descriptive statistics reported in the Results section of each study. Values of Cohen’s $d$ less than or equal to .20, .50, and .80 were interpreted as small, moderate, and large effect sizes, respectively (32). The overall pooled effect sizes ($d_w$) for each mental health outcomes were estimated using the weighted mean of $d$ value for each study (33, 34). The 95% confidence interval (CI) was computed, as was its significance according to the ratio of pooled effect size to the standard error (33, 34). Pooled effect sizes were estimated whenever at least three independent studies yielded data. Heterogeneity in effect sizes was computed using the $Q$ statistic (34) and $I^2$ index (14, 35). Excel was used to compute these metrics.

Despite the small number of studies for each outcome, Egger’s regression (i.e., the standard normal deviate [SND] is regressed against the estimate’s precision, defined as the inverse of the standard error; $SND = a + b \times \text{precision}$) (36) was performed to detect publication bias. These analyses were conducted using SPSS 22.

Risk of Bias
The current systematic review assessed quality of studies included using the rating scale developed by the National Institutes of Health for observational cohort and cross-sectional research designs (37). This scale is composed of 14 items rated on three levels (i.e., Yes; No; Cannot determine/Not applicable/Not reported [CD, NA, NR]) where a “no” or “undetermined” response indicates the presence of possible bias. The quality of each study was independently assessed by two authors (GP and FG), who reached a high inter-rater agreement.

| Study               | $N_{exposed}$ | $N_{not\ exposed}$ | $d$ (95% CI)      | Forest plot |
|---------------------|---------------|---------------------|-------------------|-------------|
| Chan & Hsu, 2004    | 108           | 555                 | .04 (-.30 – .37)  |             |
| Lin et al., 2007    | 69            | 26                  | .15 (-.30 – .61)  |             |
| Sim et al., 2004    | 97            | 180                 | .07 (-.18 – .32)  |             |
| Summary             | 271           | 761                 | .07 (-.11 – .25)  |             |

**FIGURE 2** | Forest plot of overall psychiatric symptoms.

| Study               | $N_{exposed}$ | $N_{not\ exposed}$ | $d$ (95% CI)      | Forest plot |
|---------------------|---------------|---------------------|-------------------|-------------|
| Chan & Hsu, 2004    | 108           | 555                 | .02 (-.32 – .35)  |             |
| Chong et al., 2004  | 249           | 1008                | .26 (.12 – .39)   |             |
| Lee et al., 2007    | 33            | 66                  | .88 (.44 – 1.31)  |             |
| Lee et al., 2018    | 196           | 163                 | .41 (.20 – .62)   |             |
| Lin et al., 2007    | 66            | 26                  | .44 (.02 – .89)   |             |
| McAlonan et al., 2007 | 71   | 113                 | .63 (.33 – .94)   |             |
| Sim et al., 2004    | 97            | 180                 | .00 (.25 – .25)   |             |
| Summary             | 820           | 2111                | .30 (.21 – .39)   |             |

**FIGURE 3** | Forest plot of PTSD symptoms.

| Study               | $N_{exposed}$ | $N_{not\ exposed}$ | $d$ (95% CI)      | Forest plot |
|---------------------|---------------|---------------------|-------------------|-------------|
| Lee et al., 2007    | 33            | 66                  | .79 (.35 – 1.22)  |             |
| McAlonan et al., 2007 | 71   | 113                 | .80 (.49 – 1.10)  |             |
| Poon et al., 2004   | 534           | 1392                | .44 (.12 – .76)   |             |
| Summary             | 638           | 1571                | .66 (.46 – .85)   |             |

**FIGURE 4** | Forest plot of depression and anxious symptoms.
### TABLE 1 | Overview of selected studies.

| Study | Sample description | Country | Disease | Study design | Timing | Assessment tools | Outcome measure | % of clinical distress | Effect size (95% CI) | Other significant findings |
|-------|---------------------|---------|---------|-------------|--------|------------------|-----------------|------------------------|-----------------------|------------------------|
| (17)  | N=661 (113 doctors; 548 nurses) | Singapore | SARS | Cross-sectional survey | 2-months after first case | GHQ-28 (cut-off > 5) IES (cut-off > 30) | Psychiatric symptoms | Psychiatric symptoms 27% (Doctors: d = .14; −.25–.53) Nursing: d = .06; −.29–.17 | Clear communication of directives/precautionary measures (p<.02) and support from supervisors/colleagues (p=.003) are protective factors. No difference between doctors and nurses. No significant difference between those who were or were not exposed to SARS patients |
| (18)  | N=1,257/676 nurses; 139 doctors; 140 health administrative workers; others health professionals | Taiwan | SARS | Cross-sectional survey | 6 weeks (during serious nosocomial infection) | Chinese Health Questionnaire (cut-off > 2) IES (cut-off not reported) | Psychiatric morbidity PTSD symptoms | 75.3% psychiatric comorbidity PTSD symptom s = .26 (12–.40) | - Differences between initial phase and second phase |
| (19)  | N=271 HCWs; N=342 HCNs | Hong Kong | SARS | Case-control study | During outbreak | PSS (cut-off not reported) | Perceived stress | Not reported | Not available data | HCWs were not more stressed than healthy control subjects |
| (20)  | N=139 (74% nurses; 15% employees; 11% clerical staff) | Toronto, Hamilton (Ontario) | SARS | Follow-up study | - one/two years after outbreak | SCID CAPS | Psychiatric disorders | 5% any new onset of a psychiatric disorder 4% new episodes of Major Depression 2% new PTSD | Any Axis I diagnosis correlates with a previous psychiatric history (p=.02) (protective) association with years of health care experience (p=.03) and perception of hospital support and training (p=.03) |
| (21)  | N=99 (63 nonhealth care workers vs 33 health care workers survivors to outbreak) | Hong Kong | SARS | Case-control study | - 1 year after outbreak | GHQ-12 (cut-off > 3) PSS-10 IES-R DASS-21 | Psychiatric morbidity PTSD symptoms Depressive and anxiety symptoms | Overall psychiatric morbidity 64% Health care workers 90.3% Nonhealth care workers 49.1% | Psychological distress d = .44 (0.33–0.55) PTSD symptoms d = .88 (0.45–1.31) Depressive symptoms d = .70 (0.27–1.13) Anxiety symptoms d = .87 (0.44–1.30) | Health care workers: > depression (p<.01), > anxiety (p=.001), > PTSD symptoms (p=.05) -77.4% of female SARS survivors scored above the GHQ-12 threshold |
| (22)  | N=359 HCW (196 nurses, 30 doctors, 55 medical | South Korea | MERS | Cross-sectional survey and case-control | During outbreak and one month after | IES-R (cut-off > 25) | PTSD symptoms | 51% | Trend differences between nurses and doctors (p=.048) | (Continued) |
| Study Sample description | Country | Disease | Study design | Timing | Assessment tools | Outcome measure | % of clinical distress | Effect size (95% CI) | Other significant findings |
|--------------------------|---------|---------|--------------|--------|------------------|----------------|------------------------|----------------------|--------------------------|
| technicians, 31 administrators, 8 pharmacists; 39 others | Taichung (Taiwan) | SARS | Case-control | -one-month after outbreak | CHQ-12 (cut-off > 3) Davidson Trauma Scale-Chinese version (cut-off > 40) | Psychiatric comorbidity PTSD symptoms Overall psychiatric morbidity PTSD symptoms | 47.7% PTSD symptoms 19.3% | Psychological distress $d = .15$ ($-.29$–$.59$) PTSD symptoms $d = .44$ ($0.00$–$.88$) | -HCW of ED showed more PTSD symptoms than HCW of psychiatric ward ($p<.05$) -No difference in CHQ PTSD symptoms ($93\%$ of medical staff considered the SARS outbreak as a traumatic experience. -having been quarantined ($p<.001$), high work exposure ($p<.001$), current stressful job ($p<.001$), high PTSD symptoms ($p<.001$) and pre-SARS trauma exposure ($p<.01$) significantly predicted high depressive symptoms.-Altruistic acceptance of SARS-related risk was negatively associated ($p=.0005$) |
| N=92 (66 HCW in emergency department vs 26 HCW in psychiatric ward) | Beijing SARS Cross-sectional survey | Case-control | Toronto vs Hamilton | -3 years after outbreak | CES-D (cut-off > 25) | Depressive symptoms | 37.5% | Psychological distress $d = .76$ ($0.47$–$.103$) Depressive symptoms $d = .76$ ($0.26$–$.102$) Anxiety symptoms $d = .84$ ($0.55$–$.113$) PTSD symptoms $d = .63$ ($0.34$–$.92$) Not available data | Maladaptive coping and perceived adequacy of training with protection and support explained 18% of the variance in burnout. - Maladaptive coping and attachment anxiety, together with a protective effect of experience in healthcare, explained 31% of the variance in psychological distress. -in 2003, equally high perceived stress levels ($p=.176$) -in 2004, perceived stress decreased only in low risk HCW ($p<.05$) -in 2004, no differences in perceived stress among doctors, nurses, and others -PTSD symptoms correlated with exposure to SARS ($p<.001$) |
| N=769 (73.5% nurses, 8.3% clerical staff, 2.9% doctors, 2.3% respiratory therapists) | Toronto, Hamilton SARS | Cross-sectional survey | Case-control | -19 months after outbreak | K10 (cut-off > 16) Maslach Burnout Inventory (cut-off > 27) IES (cut-off > 26) | Psychological distress Burnout PTSD symptoms Psychological distress Burnout PTSD symptoms Psychological distress Burnout PTSD symptoms | 37.5% 24.8% 11.1% | Psychological distress $d = .34$ ($13$.–$.55$) Burnout $d = .33$ ($12$.–$.54$) PTSD symptoms $d = .31$ ($0.00$–$.62$) | No available data |
| N=184 (71 high-risk HCW and 113 low-risk) (2004) | Hong Kong | SARS | Case-control study | -during (2003) and one year (2004) after outbreak | PSSS-10 DASS-21 IES-R | Psychological distress Depressive anxious symptoms PTSD symptoms Not reported | Psychological distress $d = .76$ ($0.47$–$.103$) Depressive symptoms $d = .76$ ($0.26$–$.102$) Anxiety symptoms $d = .84$ ($0.55$–$.113$) PTSD symptoms $d = .63$ ($0.34$–$.92$) Not available data | Psychological distress $d = .76$ ($0.47$–$.103$) Depressive symptoms $d = .76$ ($0.26$–$.102$) Anxiety symptoms $d = .84$ ($0.55$–$.113$) PTSD symptoms $d = .63$ ($0.34$–$.92$) Not available data | -in 2003, perceived stress levels ($p=.176$) -in 2004, perceived stress decreased only in low risk HCW ($p<.05$) -in 2004, no differences in perceived stress among doctors, nurses, and others -PTSD symptoms correlated with exposure to SARS ($p<.001$) |
| N=510 | Toronto SARS | Cross-sectional survey | Case-control | -during outbreak | GHQ-12 (cut-off > 3) | Psychiatric symptoms | 29% | Not available data | -45.1% nurses, 33.3% allied health care professionals, 17.4% |

(Continued)
reliability (Cohen’s k = .89). At the end of the evaluation, ratings of each study were summed up within each item in order to provide a quantitative approach to the assessment of risk of bias. Given the number of studies included in this review, the total score (i.e., 210) was divided in three subscales capturing strengths (i.e., Yes responses), biases (No responses) and qualities not applicable (NA response). For a detailed description of results of these procedures, see Table 4.

RESULTS

A total of 7,393 HCWs has been scrutinized by the all studies (Table 1). Descriptive analysis of the all studies are reported in Table 2. Data are drawn from survey with voluntary and anonymous participation with a response rate ranging from 19.9% to 92%. Only one study (20) determined the clinical picture of participants by a diagnostic interview by DSM criteria (12). The most part of the studies (17–19, 22, 23, 26–29) measured the level of psychological distress during or immediately after the outbreak. From 9.6% to 51% of HCWs reported symptoms of PTSD and from 20% to 75% reported the prevalence of anxiety and depression, respectively. The other studies (20, 21, 24, 30) rated psychological distress from one to three years after outbreak. PTSD symptoms were detected from 2% to 19% and from 5% to 90% reported psychiatric symptoms at follow-up. One study (38) reported in 19%–30% of HCW's significant levels of burnout. Only one study (19) comparing HCWs and healthy subjects did not report significant findings on the self-rating of perceived stress level. Only few studies compared the psychological burden of the outbreak comparing doctors and nurses: three did not find any differences (17, 26, 29), two reported a higher occurrence in nurses (28, 37) and the last one (22) a trend for nurses (Table 1).

TABLE 1 | Continued

| Study | Sample description | Country | Disease | Study design | Timing | Assessment tools | Outcome measure | % of clinical distress | Effect size (95% CI) | Other significant findings |
|-------|-------------------|---------|---------|-------------|--------|------------------|-----------------|-----------------------|------------------------|--------------------------|
| (28)  | N=1926 (813 nurses; 141 doctors; 349 supporting staff; 230 administrative staff; 207 allied health workers; 186 others) | Hong Kong | SARS | Case-control Front-line health care workers vs Administrative Controls Contact with SARS Vs No contact with SARS | -two months during outbreak | STAI Maslach Burnout Inventory | Anxiety Burnout score | Not reported | Anxiety symptoms $d = .41$ (−0.2–0.84) $d = .47$ (−0.02–0.91) Burnout $d = .61$ (−0.19–1.03) | - Anxiety was higher among front-line HCW than administrative staff controls ($p<.001$). - Anxiety scores correlated ($p<.001$) with burnout scores among front-line HCW ($r=0.58$), controls ($r=0.52$), staff with contact with SARS patients ($r=0.59$), and staff without contact ($r=0.58$). - No differences between doctors and nurses in the outcome measures |
| (29)  | N=277 (91 doctors and 186 nurses) | Singapore | SARS | Cross-sectional survey Case-control study Direct exposure vs indirect exposure | 4 months after outbreak | GHQ-28 (cut-off > 5) IES-R (cut-off > 3) | Psychiatric morbidity PTSD symptoms 20.6% PTSD symptoms 9.6% | Psychiatric morbidity PTSD symptoms | Psychological distress $d = .07$ (−0.18–0.32) PTSD symptoms $d = .00$ (−0.25–0.25) | - Nurses reported higher morbidity rates |
| (30)  | N=124 (41 doctors and 83 nurses) | Singapore | SARS | Cross-sectional survey | -6 months after outbreak | GHQ-28 (cut-off > 5) IES (cut-off > 26) | Psychiatric morbidity PTSD symptoms 18.8% PTSD symptoms 17.7% | Psychiatric morbidity PTSD symptoms | Not available data | - Nurses reported higher morbidity rates |
| (31)  | N=549 hospital employees | Beijing | SARS | Cross-sectional survey | 3 years after outbreak | IES-R (cut-off >20) PTSD symptoms | PTSD symptoms | Not available data | - Psychiatric symptoms continue to show symptoms after three years - altruism correlate with low PTSD |

CAPS, Clinician-Administered PTSD Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CHQ-12, Chinese Health Questionnaire-12; DASS-21, 21-item Depression Anxiety Stress Scales; ED, Emergency Department; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HCW, Health Care Workers; IES, Impact of Event Scale; MER, Middle East respiratory syndrome; MINI, Mini International Neuropsychiatric Interview; K10, Kessler Psychological Distress Scale; PSS-10, 10-item Perceived Stress Scale; SARS, Severe Acute Respiratory Syndrome; SCID, Structured Clinical Interview for DSM-IV; STAI, State-Trait Anxiety.
Some studies (17, 20, 24, 26, 38) analyzed the buffering factors for the burden of outbreak on psychological distress. Protective factors were clear communication of directives/precautionary measures, support and training from supervisors/colleagues, years of health care experience and altruism; risk factors for depression were having been quarantined, high work exposure, current stressful job, high PTSD symptoms and pre-SARS trauma exposure.

Considering aggregated results, eight studies showed that up to 35% (95% CI: 19.17–52.67) of HCWs reported clinically significant levels of general psychiatric symptoms during and after pandemic emergency. Interestingly, pooled effect size (dw = .07 [-.11–.26]) did not highlight significant differences between HCWs who were and were not directly involved in addressing medical emergency. This evidence was consistent across studies included (Q (2) = .16; ns; I² = .00%). With respect to PTSD symptoms, the analyses found that 17% (95% CI: 7.02–27.47) of HCWs developed clinically significant symptoms of this condition. Furthermore, the direct involvement in the management of pandemic emergency significantly affected the severity of PTSD symptoms (dw = .30 (.21–.39); p < .001), even though the heterogeneity across studies were large (I² = 72.05%) and significant (Q (6) = 27.41; p < .01). Overall, clinically significant depressive and anxious symptoms were reported by up to 6% (95% CI: 7.02–27.47) of HCWs. Nevertheless, the HWCs who were directly involved in addressing pandemic emergency showed significantly higher depressive and anxious symptoms (dw = .66 (.46–.85); p < .001) than ones who were not directly exposed to the medical emergency. This finding was consistent across studies (Q (2) = 2.93; ns; I²= 31.78%).

Ultimately, Egger’s regression coefficients did not detect bias of publication for the previous indexes (Table 3). Table 4 reported the rating of the risk of bias. Overall, the reviewed studies showed specific weaknesses in the participation rate, definition and measurement of exposure, and control of confounding variables. Anyhow, we must bear in mind that these real-world studies were performed in emergency contexts, and therefore their quality is acceptable though just sufficient from a methodological point of view.

### Table 2 | Summary of descriptive statistics of studies included (N = 15).

| Variable | N  | %   |
|----------|----|-----|
| Total sample | 7,766 |
| Doctors | 577 | 7.4 |
| Nurses | 3,171 | 40.8 |
| Other health care workers | 1,306 | 16.8 |
| Not specified | 2,712 | 35.0 |
| Singapore | 3 | 20.0 |
| Taiwan | 2 | 13.3 |
| Hong Kong | 4 | 26.7 |
| Canada | 3 | 20.0 |
| South Korea | 1 | 6.7 |
| Beijing | 2 | 13.3 |
| SARS | 14 | 93.3 |
| MERS | 1 | 6.7 |
| Cross-sectional and case-control | 7 | 46.7 |
| Cross-sectional | 4 | 26.7 |
| Case-control | 4 | 26.7 |
| General psychiatric symptoms | 8 | 53.3 |
| PTSD symptoms | 10 | 66.6 |
| Depression and anxiety symptoms | 4 | 26.7 |
| General psychological distress | 4 | 26.7 |
| Burnout | 2 | 13.3 |
| Mean of clinically relevant psychiatric symptoms | 8 | 35.92 |
| Mean of clinically relevant PTSD symptoms | 8 | 17.24 |
| Mean of clinically relevant depression and anxiety symptoms | 2 | 6.4 |

### Table 3 | Pooled effect sizes concerning the effects of direct exposure to pandemic emergency.

| Outcome | N direct exposure | N control subjects | N studies | dw (95% CI) | Q (df) | I² | Egger’s coefficient (95% bootstrap CI) |
|---------|-------------------|-------------------|-----------|-------------|--------|----|------------------------------------------|
| Overall psychiatric symptoms | 271 | 761 | 3 | .07 (-.11–.26) | .16 (2) | .00% | .58 (NE); ns |
| PTSD symptoms | 624 | 1,948 | 7 | .30 (.21–.39)** | 27.41 (6)** | 72.05% | 1.56 (–25.28–10.39); ns |
| Depression and anxiety symptoms | 638 | 1,571 | 3 | .66 (.46–.85)*** | 2.93 (2) | 31.78% | 2.15 (NE); ns |

**p < .01; ***p < .001; NE, not estimated.
which have been diagnosed by a range of 20%–50% of health care professionals. However, IES is a self-administered symptom scale to screen symptoms of PTSD. In addition, only one study (20) performed a vis-à-vis structured diagnostic interview and only 2% of subjects had a definite PTSD diagnosis after one year.

Possible psychopathological consequences of stress exposure include both specific sequelae (i.e. Adjustment Disorder, Acute Stress Disorder, Post-Traumatic Stress Disorder) and common mental disorders (e.g. Major Depressive Disorder, Generalized Anxiety Disorder, Substance-Related Disorders). Moreover, the emergence of a clinical condition among distressed individuals can be a new onset condition as well as a recurrence of previous disorders; finally, comorbid personality traits may play a role in the development of psychopathology among other predisposing factors (10). It is clear that a complete psychopathologic work-up should proceed with clinical interviews and psychometric tests, and self-administered tests on a voluntary basis may give only screening information. For this reason, we need studies assessing mental health of HCWs in a direct way, eventually adopting the cut-off of the screening tests to candidate people to the traditional procedure. Another critical point is the relevance of making follow-up study, because the cross-sectional design of most studies does not allow any prevision on the evolution of the clinical situation.

A rapid review on HCWs involved in COVID-19 pandemic (39) evidenced significant levels of distress, anxiety, depression and insomnia. Our study on previous coronavirus outbreaks adds a critical point, because we quantified the role of direct exposure to the risk of contagion (Table 3): if all HCWs showed a somewhat associated risk of developing psychiatric symptoms during outbreaks, only those in frontline showed a significant increased level of anxiety/depression and (then) PTSD. The wider study on HCWs involved in COVID-19 (40) had been performed in 34 hospitals of China and involved 1257 health care workers (68.7% response rate), with overall, 50.4%, 44.6%, 34.0%, and 71.5% of all participants reported symptoms of depression, anxiety, insomnia, and distress, respectively. The role of sleep disruption needs more studies, for the well-known link with psychopathology (41). Moreover, we need studies analyzing protective factors (both as institutional and personal ones) from the psychiatric outcome, to implement strategies of prevention.

A critical question is whether the health care workers who participated in these studies are representative of the entire population of HCWs. Unfortunately, almost all studies recruited convenience samples from well-defined, though small, populations reasonably due to this peculiar real-world research context. Beyond obvious problems of statistical power, sources of bias can be found in the insufficient measurement of the amount of exposure and in a poor evaluation of confounding variables (e.g. other sources of stress apart from working or not in high-risk settings, previous personal career, and so on). On the positive side, the reviewed studies highlight that evidence is not too dissimilar in various parts of the world, despite cultural and organizational differences. The most part of the studies adopted the Impact of Events Scale (IES) to detect PTDS symptoms, which have been diagnosed by a range of 20%–50% of health care professionals. However, IES is a self-administered symptom scale to screen symptoms of PTSD. In addition, only one study (20) performed a vis-à-vis structured diagnostic interview and only 2% of subjects had a definite PTSD diagnosis after one year.
Some evidence exists that altruistic acceptance of the own role (24) and institutional support and training (38) may have a role in buffering the psychopathologic outcomes. However, we need more studies on resilience factors in HCWs. Given the adverse impacts of experiencing burnout, psychological distress in the workplace, it is of great importance to investigate the potential factors and mechanisms that could enlighten the improvement of the mental health and maintenance of adequate proficiency of HCWs in the midst of the pandemic. The role of the spouses and/or familial support, capacity of self-help and using mindfulness techniques to cope with distressing situations, personality characteristics, institutional facilities (e.g. mental health support, availability of medical supplies) deserve further studies. Moreover, we need to address factors bolstering resilience. Among all the influential factors, social support is one of the protective factors for mental health for HCWs (44–46). A strong social support network can buffer feelings of isolation, strengthening resilience. Video calls and virtual meetings (or on-line group support) allow for maintenance of social relations while preserving physical distancing.

Other moderating interventions include delivery of general and medical supplies, limiting isolation to the shortest duration necessary, and emphasizing altruism as core value of the profession as much as a strong leadership with clear, honest and open communication to balance fears and uncertainties (47).

Proposals for delivering psychological support exist (48), with better chance of achieving psychological interventions when clinical psychology units are available within the hospitals (a rarity in Italy). Telemedicine may be an opportunity for offering supportive interventions intended to promote wellness and boost coping strategy (such as empathic listening, psychoeducation or supportive therapy) (47).

In synthesis, our review showed an association with a likely negative burden for mental health of HCWs in terms of PTSD symptoms and other psychopathology (anxiety, depression, psychological distress) both in the acute phase and, in some cases, after a time interval. Learning lessons from the current pandemic outbreak is imperative to prepare better strategies for new healthcare management models for the next generations of doctors, nurses and staff of health-care services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

FG and RF ideated, wrote and called to collaborate the co-authors. GIP contributed to the theoretical building of the paper and wrote the parts on psychiatric issues, with a contribution in the selection of papers and quantification of the risk of bias. FR and FM made the bibliographic search. MC made the statistical analysis, giving some of the methodological indications. GaP, GS, MPC, AP supervised the all work, read and approved the manuscript. All authors contributed to the article and approved the submitted version.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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