Dear Editor,

Pneumothorax and pneumomediastinum may complicate acute respiratory distress syndrome (ARDS). Early studies in ARDS caused by coronavirus disease 2019 (COVID-19) suggested increased pneumothorax incidence but lacked relevant controls [1, 2]. We investigated whether COVID-19 ARDS is associated with more radiographic pneumothorax and/or pneumomediastinum than pre-pandemic ARDS and whether pneumothorax/pneumomediastinum in COVID-19 ARDS is associated with worse outcomes or differing treatments.

This retrospective cohort study included adult ARDS patients admitted between 2017 and 2021 to a 23-hospital system in the Intermountain West. We abstracted data from the electronic health record and used natural language processing to identify radiographic pneumothorax and/or pneumomediastinum [3, 4]. We performed bivariate and adjusted analyses to compare patients with pre-pandemic ARDS (2017–2020) to patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) result proximate to ARDS (2020–2021) (see also Supplemental Methods).

Comparing 2,211 patients with COVID-19 ARDS and 5,522 with pre-pandemic ARDS (Table 1 and Supplemental Fig. 1), unadjusted incidence of pneumothorax/pneumomediastinum was similar (24% vs. 22.5%, p < 0.148). After adjustment, pneumothorax/pneumomediastinum risk was significantly higher in COVID-19 vs. pre-pandemic ARDS (adjusted odds ratio 1.31, 95% CI 1.13–1.52, p < 0.001). COVID-19 ARDS patients had significantly higher rates of pneumomediastinum but not pneumothorax in unadjusted and adjusted analyses (Table 1 and Supplemental Table 2). Compared to COVID-19 ARDS, chest tube placement for pre-pandemic pneumothorax patients was more frequent (52.1% vs. 38.2%, p < 0.001), occurred earlier (−0.4 vs. 1.3 days, p < 0.001) and remained in place longer (9.9 days vs. 7 days, p < 0.001).

Mortality rates in COVID-19 ARDS were higher than pre-pandemic ARDS (39.4% vs. 28.5%, p < 0.001). Among COVID-19 ARDS patients, we observed higher 30-day mortality rates with pneumothorax/pneumomediastinum (49.5% vs. 36.2%, p < 0.001), while we observed a lower mortality in pre-pandemic ARDS patients with pneumothorax/pneumomediastinum (24.8% vs. 29.5%, p < 0.001). Adjusted analyses yielded similar results (Supplemental Table 3).

Prior to pneumothorax/pneumomediastinum, both COVID-19 and pre-pandemic ARDS cohorts had similar receipt of invasive mechanical ventilation (77% vs. 74%, p = 0.17). COVID-19 patients received higher maximum PEEP (16 vs. 10 mmHg, p < 0.001). The median duration of invasive ventilation prior to pneumothorax/pneumomediastinum was much longer in the COVID-19 patients (2 vs. 0.3 days, p < 0.001; Supplemental Fig. 2), as was time from admission until pneumothorax/pneumomediastinum (7.3 vs. 1.3 days, p < 0.001).
Study strengths include comparison of large, multi-hospital COVID-19 and control ARDS cohorts. Limitations include the possibility of unmeasured confounding and potentially counting radiographic pneumothorax/pneumomediastinum events that were "clinically insignificant" or not due to acute lung injury. We note a substantially higher rate of pneumothorax/pneumomediastinum compared with other published cohorts (Supplemental Table 5). Our detection is more sensitive than clinically reported as all events are included, not just pneumothorax/pneumomediastinum > 2 cm or presence in clinical notes, which may limit generalizability. The relationships between radiographic and clinically significant pneumothorax/pneumomediastinum, pneumothorax/pneumomediastinum risk factors (including use of guideline-endorsed “high positive end-expiratory pressure (PEEP)” ventilation [5]), and pneumothorax management warrant further study.

In conclusion, COVID-19 ARDS patients experienced similar rates of radiographic pneumothorax but more pneumomediastinum. Chest tubes were used less frequently and placed later in COVID-19 ARDS than in pre-pandemic ARDS. Radiographic pneumothorax/
Table 1 (continued)

|                                | Overall | Prepandemic | p    | Overall | Prepandemic | p    | Overall | Prepandemic | p    |
|--------------------------------|---------|-------------|------|---------|-------------|------|---------|-------------|------|
|                                | COVID-19| Prepandemic |      | COVID-19| Prepandemic |      | COVID-19| Prepandemic |      |
| Invasive mechanical ventilation| 872 (39.5) | 2902 (52.6) | < 0.001 | 639 (38.1) | 2194 (51.3) | < 0.001 | 233 (43.9) | 708 (57.3) | < 0.001 |
|                               |         |             |      |         |             |      |         |             |      |
| **Outcomes**                   |         |             |      |         |             |      |         |             |      |
| Pneumomediastinum              | 288 (13) | 188 (3.4)   | < 0.001 | 288 (54.2) | 188 (15.2) | < 0.001 |
| Pneumothorax                   | 448 (20.3) | 1201 (21.7) | 0.158 | 448 (84.4) | 1201 (96.9) | < 0.001 |
| Pneumothorax or pneumomediastinum | 531 (24) | 1240 (22.5) | 0.148 |         |             |      |         |             |      |
| Days from admission until pneumothorax or pneumomediastinum | 7.3 [2.9, 12.6] | 1.3 [0.1, 5.1] | < 0.001 | 7.3 [2.9, 12.6] | 1.3 [0.1, 5.1] | < 0.001 |
| Hospital Length of Stay (days) | 14.5 [9.5, 23.7] | 9.2 [5.3, 15.4] | < 0.001 | 13.1 [8.9, 21] | 8.3 [4.9, 13.6] | < 0.001 | 20.8 [12.8, 33.4] | 13.9 [8.4, 21] | < 0.001 |
| 30 Day Mortality               | 871 (39.4) | 1572 (28.5) | < 0.001 | 608 (36.2) | 1265 (29.5) | < 0.001 | 263 (49.5) | 307 (24.8) | < 0.001 |
| ICU Length of Stay             | 10.4 [6, 18.4] | 4.9 [2.5, 9.9] | < 0.001 | 9 [5.2, 15.2] | 4.3 [2.2, 8.6] | < 0.001 | 17.1 [10.1, 27.3] | 7.9 [4, 14.4] | < 0.001 |
|                               |         |             |      |         |             |      |         |             |      |
| **Management of pneumothorax and/or pneumomediastinum** |         |             |      |         |             |      |         |             |      |
| Chest tube placed              | 203 (38.2) | 646 (52.1) | < 0.001 |         |             |      |         |             |      |
| Days from admission until chest tube placement | 8.6 [3.9, 15.9] | 0.9 [0.2, 3.8] | < 0.001 |         |             |      |         |             |      |
| Duration of chest tube (days)  | 9.9 [4.9, 17] | 7 [4.1, 11.5] | < 0.001 |         |             |      |         |             |      |
|                               |         |             |      |         |             |      |         |             |      |
| **Treatment occurring prior to pneumothorax/pneumomediastinum** |         |             |      |         |             |      |         |             |      |
| Nasal canula utilized          | 228 (44) | 598 (56.5) | < 0.001 |         |             |      |         |             |      |
| High-flow nasal canula utilized| 402 (77.6) | 179 (16.9) | < 0.001 |         |             |      |         |             |      |
| Non-invasive ventilation utilized | 251 (48.5) | 368 (34.8) | < 0.001 |         |             |      |         |             |      |
| Invasive ventilation utilized  | 400 (77.2) | 783 (74) | < 0.001 |         |             |      |         |             |      |
| Positive pressure ventilation  | 481 (92.9) | 918 (86.8) | < 0.001 |         |             |      |         |             |      |
| Nasal canula days              | 0 [0, 0.9] | 0.2 [0, 2] | < 0.001 |         |             |      |         |             |      |
| High-flow nasal canula         | 0.6 [0, 3.5] | 0 [0, 0] | < 0.001 |         |             |      |         |             |      |
| Non-invasive ventilation days  | 0 [0, 0.7] | 0 [0, 0.3] | < 0.001 |         |             |      |         |             |      |
| Invasive ventilation days      | 2 [0, 8.4] | 0.3 [0, 2.6] | < 0.001 |         |             |      |         |             |      |
| Maximum FiO₂                    | 100 [100, 100] | 100 [65.5, 100] | < 0.001 |         |             |      |         |             |      |
| Maximum PEEP                   | 16 [14, 20] | 10 [8, 12] | < 0.001 |         |             |      |         |             |      |
| Maximum plateau pressure        | 34 [30, 40] | 24 [19, 30] | < 0.001 |         |             |      |         |             |      |
| Maximum peak inspiratory pressure | 38 [28, 45] | 29 [23, 36] | < 0.001 |         |             |      |         |             |      |
pneumomediastinum in COVID-19 ARDS patients is associated with an increased mortality.

Supplementary Information
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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Daniel Knox. The first draft of the manuscript was written by Alex Brunhoeber and Daniel Knox and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
To protect patient privacy and comply with relevant regulations, identified data are unavailable. Requests for deidentified data from qualified researchers with appropriate ethics board approvals and relevant data use agreements will be processed by the Intermountain Office of Research, officeofresearch@imail.org.

Declarations
Conflicts of interest
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