

## Incidence Rate of ALI in COVID-19 Patients

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### ABSTRACT

**Background:** With the outbreak of COVID19, acute lung injury has been detected as the main etiology for intensive care admission and high mortality rate. Among the infected population, there is some percentage of those who tend to develop acute respiratory distress syndrome and respiratory failure. Thus, the intensivist and anesthesiologist must be aware of the of incidence rate of acute respiratory distress syndrome (ARDS), risk factors, and try to take measures to reduce its incidence.

To define the rate of incidence of acute lung injury and ARDS among COVID 19 patient.

**Methods:** We performed a narrative review via searching in three databases PubMed, Google Scholar and Embase for all studies that mentioned the incidence of acute lung injury among infected patients with COVID19, manual searching also completed. All the selected reviews were limited to the English language and data also.

**Results:** Five searches referred to the exact number of patients and the percentage rate of incidence of ARDS related to COVID 19 infection, other articles are merely reviews and case reports.

**Conclusion:** Incidence of acute lung injury among COVID19 patient was highly reported, and some percentage of these cases tend to develop ARDS especially in those who have preexisting diseases and obesity.

Acute lung injury and "acute respiratory distress syndrome" were first depicted in 1967 by Ashbaugh and his colleagues, and are marked by sudden initiation of clinically significant hypoxemia and the existence of diffuse pulmonary infiltrates [1]. These infiltrates showed on the radiograph as pulmonary edema consequential from elevated pulmonary vascular permeability [2]. ARDS is a form of lung injury that commonly happens in response to multiple affecting events and is characterized by inflammation, elevated permeability of pulmonary vasculature, hypoxemia, stiff lungs, and losing of aerated lung tissue [3]. Until recently, the most accepted description of ARDS for use in the clinical setting is the Berlin definition of ARDS published in 2013. According to that, ARDS was figured out as: the acute diffuse, inflammatory lung injury followed by elevated pulmonary vascular permeability [3]. In addition to increasing the lung weight, acute

hypoxemia and a ratio of arterial oxygen partial pressure to the oxygen portion of motivated air less than or equal to 300mm Hg on positive end-expiratory pressure greater than or equal to 5cm H<sub>2</sub>O [3].

These findings are associated with the bilateral spreading of opacities on radiology that is not otherwise clarified fully by fluid overload or heart failure [3]. Acute lung injury and ARDS represent the most severe complications of the viral infection sustained by coronavirus disease 2019 (COVID- 19) [2]. A novel RNA coronavirus COVID-19 identical to SARS-CoV and (MERS-CoV) [4]. Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, was identified to an etiology of pneumonia [5]. In January 2020, influencing Wuhan city, the capital of Hubei province, from there it quickly extended across China. After infecting and producing the mortality of thousands of individuals in China, the virus has extensively spread to

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Italy and other countries in Europe and the USA, with the numbers of confirmed cases, presently rising each day [6].

## Methods

This narrative review was started after obtaining approval from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.51947). We searched the present literatures published on Embase, PubMed, and Google scholar. Furthermore, citation review and hand search of new journals related to acute lung injury and COVID 19-associated ARDS were searched. The published studies from December 2019 until the end of September 2020 were searched. The following keywords: COVID19, Acute lung injury, and ARDS were executed. The study involved an age group 18-90 years and included 50 published studies, which are 4 case series, 3 nonrandomized clinical studies, 3 systematic reviews and 40 review articles. Five articles mentioned the patient's number and percentage rate of incidence of ARDS in COVID 19 patients. All the reviews we have selected were limited to the English language. The exclusion criteria included all the studies that had inappropriate topics, were not pertinent to the focused purpose of the study and all articles in other languages. The main goal was to review the studies about the rate of incidence of acute lung injury particularly ARDS related to COVID 19 infection and measures to reduce its incidence.

## Clinical manifestations

There is higher variability regarding clinical presentations between asymptomatic to severely affected patients. However, the initial symptoms were highly evidenced to appear after four to five days from exposure, and the incubation term generally within 2 weeks [7-9]. Records from 181 confirmed cases in China with identifiable exposures, one modeling study showed that symptoms developed within 2.2 days in 2.5%, and within 11.5 days in 97.5% of infected individuals [10].

Viral loads may reach their peak for a minimum of 8 days and a median of 20 days from symptom onset [6]. Another cross-sectional study from 1084 patients, suggested a longer median incubation period of 7.8 days, and about 10 percent of COVID-19 patients did not develop symptoms until 14 days after exposure [11].

The initial presentations included; headache, dyspnea, fever, myalgias, and cough [5]. Other features included; diarrhea, sore throat, and smell or taste insults [12]. Pneumonia is reported as the most frequent serious sign of COVID19 infection initially manifested by coughing, fever, dyspnea, and bilateral infiltrates on the chest radiography [9,13-14]. Some clinical presentations (particularly smell or taste abnormalities) more frequently noticed with COVID-19 than with other viral respiratory infections [15]. Dyspnea after one week of the

primary symptoms can be considered as an indicative presentation of COVID19 [13]. The associated symptoms were documented in range by reporting of 373,883 confirmed cases with COVID19 in the center of disease control (CDC) in the united states; Cough in more than 50%, Fever  $>38^{\circ}\text{C}$  in 43 percent, Myalgia in 36 percent, Headache in 34 percent, Dyspnea in 29 percent, Sore throat in 20 percent, Diarrhea in 19 percent, Nausea/vomiting in 12 %, and Loss of smell or taste, abdominal pain, are reported to be  $<10$  percent for each [16]. These clinical manifestations are also reported in other cohort studies at a similar range [15] [16]. Of note, fever is not a universal finding, however, in some studies, it is reported in a high percentage of populations approximately 69% [17].

In addition, other cohort studies illustrate this finding involved almost all the patients but approximately 20 percent had a very low-grade fever  $<100.4^{\circ}\text{F}/38^{\circ}\text{C}$  [13].

Smell and taste abnormalities were reported at a high rate by some studies [18-19]. Furthermore, another study of 202 patients with COVID19, smell and taste alteration have been reported in 64% of patients, severely was in 24% of patients, as well as these changes revealed as the only symptoms in 3% and high frequently exist than other symptoms among the remaining 12% [18]. Gastrointestinal symptoms were not reported commonly among confirmed cases, However, diarrhea, nausea, and vomiting were reported in 8,2,1 % respectively in a cohort study of 50 patients, and in 21% of 300 patients for all GIT symptoms in other study [12,17]. Anorexia also reported in approximately 3%, 10 % among patients outside ICU and inside ICU respectively [2]. Respiratory rate (mean) was 20 breath/ min, Heart Rate (mean) 88.37 in 15%, Systolic/diastolic pressure (mean) 126.10/79.60 in 10 %, 15%, 12% respectively, of total admissions [2]. Conjunctivitis also reported in one study [20]. Initial occurrence of complications mandate hospitals admission with potential basic care inclusion, a situation that may lead to a rapid worsening in the clinical state and an acute worsening of respiratory failure within the first 7 days of primary symptoms [21]. Common laboratory findings in patients with positive RT-PCR including; lymphopenia, elevated amino transaminase levels, elevated lactate dehydrogenase levels, as well as elevation of inflammatory markers (eg, ferritin, C-reactive protein, and ESR), and abnormalities in coagulation tests with an elevation of coagulation markers such as D-dimer and fibrinogen [5,15].

Chest radiographs are considered a non-specific criterion in the diagnosis of COVID19 as well as it may be normal in a high percent of confirmed cases [2]. However, the most Common radiological abnormalities detected among patients with COVID19 including; alliance and ground-glass opaqueness, with bilateral, peripheral, and lower lungs zone distribution; lungs

involvement increased over the course of the disease, with a peak in severity at median 10.5 days after symptoms onset [22].

### Acute Lung Injury And Ards In Covid-19 Patients

The incidence and severity of ALI were reported as major prognostic factors for the deterioration of patients with COVID-19 infection [2,23]. The mechanism of inducing of ALI in COVID19 include diffuse alveolar damage, massive production of inflammatory mediators, an elevated vascular permeability, and hyaline membrane formation, thus causing progressive hypoxemia, and lung fibrosis toward the healing phase [24-25]. The patients admitted to the ICU with confirmed COVID-19's pneumonia and some of them ARDS, are those patients who met Berlin 2012 criteria of ARDS [26-27]. These criteria include; the acute onset of respiratory failure, or new worsening symptoms within 1 week, bilateral opacities on chest x-ray, computed tomography, or ultrasound that is not fully defined by effusions, lobar or lungs collapse, or nodules. Additionally, the origin of edema is not attributed to cardiac failure in acute hypoxemic respiratory failure lung abnormalities seen in X-rays, CT scans, or MRIs in the occurrence of hypoxia [3,24]. Notably, this complication, which is often presented on average 8–12 days after the onset of severe symptomatology, might lead to ARDS even 2 days from hospital admission. Therefore, the onset time may be inconsistent with that published in Berlin 2012 criteria of typical ARDS [24-25].

One of the distinctive characteristics of COVID19 ARDS is that hypoxia is not associated with pulmonary atelectasis, as well as ventilator mechanics and pulmonary compliance are often well preserved in high percentage of patients [25,27-28]. Arterial oxygen partial pressure (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio is considered to be one of the most significant parameters for ARDS diagnosis and classification as it is easy to be performed and analyze [29]. The severity Of ARDS was categorized according this parameter into three categories after applying  $peep \geq 5$ cm H<sub>2</sub>O; mild ( $200 \leq PaO_2/FiO_2 \leq 300$ mm Hg) Moderate  $150 \text{mm Hg} \leq PaO_2/FiO_2 < 200$  mm HG), severe ( $PaO_2/FiO_2 \leq 100$ mm HG) [29]. The hypoxemic respiratory failure and ARDS observed in COVID-19 range from mild to severe [29].

Respiratory rate and arterial oxygen saturation are two important parameters for judging patients clinical condition and allowing early recognition of ARDS, subsequently  $RR \geq 30$  breath/min,  $SpO_2 \leq 92\%$  may indicate severe disease and require further evaluation [24]. Coagulation disorders most commonly detected among COVID19 ARDS patients including; micro vascular thrombosis (particularly in fatal cases), pulmonary embolism is also highly reported in patients

with COVID19 ARDS than patients with ARDS by other causes [30].

### Risk factors

Many risk factor linked to the development of ARDS among COVID19 pneumonia cases have been reported in most studies. In a retrospective cohort study of 201 patients with confirmed pneumonia, 84(41.8%) patients developed ARDS, the major factor indicated are preexisting comorbidities including, hypertension 23 of 84 [27.4%] patients, and 16 of 117 [13.7%] patients without ARDS, diabetes mellitus 16 of 84 [19.0%] patients and 6 of 117 [5.1%] patients, respiratory diseases, and obesity are the highest consistency with ARDS development [31]. Fever was connected with the development of ARDS and also linked with better outcomes [31]. Old age, high level of D-dimer, C-reactive protein, neutrophilia organ, coagulation dysfunction, and high fever were more related to ARDS development and progression from ARDS to death [31]. Older age was associated with a great risk of developing ARDS and death; this may be attributed to a less vigorous immune response [6]. Furthermore, another cohort study of 50 hospitalized patients has shown the results in (Table 1), where, Hypertension was reported among patients with ARDS (67% v 73%) in patients without ARDS, Diabetes mellitus (63% v 54%). Of note, the male gender is believed to link with high expression of ACE2, which facilitates the virus entry to the healthy cells as one of the main components of ARDS pathophysiology [32]. Hypertension and cardiovascular disease influence the outcome, but the mechanism remains uncertain [33].

### Results

After obtaining 50 searches from 3 data basis on the recent COVID- 19 pandemic and read it extensively, we noticed that 5 articles illustrate the exact number of patients and the percentage rate of incidence of ARDS related to COVID 19 infection, other articles are only review and case report (table 1). Findings of study stated that the global literature survey of seventeen clinical studies reporting from 2486, (2212 with complete data) COVID19 hospitalized patients in five countries (Germany, USA, China, ITALY, South Korea) since the starting of the COVID-19 pandemic in January until the end of July 2020, The statistics show that among hospitalized COVID 19 patients, approximately 33% developed ARDS, 26 percent required transfer to an ICU, 16 percent received IMV, and 16 percent died. For COVID-19 patients transferred to an ICU, nearly 63 percent recieved IMV and 75 percent had ARDS. The mortality rate in COVID-19-linked ARDS is 45%, and the incidence of ARDS among non-survivors of COVID-19 was 90%(23). A study in KSA showed case series

study of 768 COVID19 patients, the mean age was 46.36±13.7, ARDS documented in 32.7% of patients, pneumonia was documented in 527 patients (68.6%) respiratory failure in 156 (20.3%) of the patients. Of note approximately 96.3% documented multiple comorbidities; D.M was the most frequent (46.4%), the main predictors for death were Male gender, ARDS, septic shock, acute kidney failure, mortality rate 4.3%, most of them are due to ARDS and respiratory failure as indicated in this study and agrees with other studies [32]. LI Liyang et al, 2020 reviewed 3375 patients with COVID-19 infection reported in 72 publications. Of these infected patients, 342 patients (10.1%) were cured in the ICU, 55 patients (21%) received invasive mechanical ventilation (30 % of them developed severe lung edema and ARDS with mortality rate 6% of the 342 ICU patients, and 1278 (37.9%) patients in regular wards (non-ICU). The onset time for the development of ARDS as mentioned by this study about 9 days from the onset of the infection which is incompatible with Berlin criteria of ARDS, Other 1755 patients were excluded due to inadequate data [2]. Chand and his team, in a cohort study of 300 patients with COVID 19 infection admitted to

ICU, ARDS was reported in 91.7%. Ninety-one percent required mechanical ventilation (47.8% of them received a period of the neuromuscular blockade), high ARDS incidence reported in this study may be attributed to that all the cases were in the ICU setting and this consistent with the concept of more than ¾ of ARDS patient

required ICU admission that is indicated in other studies [17]. Eastin et al (Eastin 2020) described the characteristics and outcomes of 21 (where 11 male, 10 female) critical ill patient with COVID 19 infection in retrospective case series. The median age was 70 (range 43-92). Approximately (85%) with comorbidities, the most common being chronic renal disease (48%), congestive cardiac failure (43%), COPD (33%), and diabetes (33%). On presentation, 52% had a fever, and (76%) reported dyspnea, [48] % had a cough. The patients developed symptoms for an average of 3.5 days before coming to the hospitals. The patients who developed ARDS was 57.1% [34]. Collectively, the total number of patients who developed ARDS is (2288) by dividing it by the total number (6676), the rate of incidence of ARDS will be 34%.

**Table 1- Risk factors associated with COVID19 ARDS development**

Variables	All patients (N=50)	ARDS patients(n=24)	Non-ARDS patients(n=26)
Age-years: median (IQR)	65 (58–76)	62 (58–70)	68 (59–81)
Female sex	73 (36.3)	9 (38)	8 (31)
Total Comorbidities	50 (100)	24 (100)	26 (100)
Hypertension	35 (70)	16 (67)	19 (73)
Diabetes mellitus	29 (58)	15 (63)	14 (54)
Pre-existing respiratory disease	25 (50)	14 (58)	11 (42)
Chronic kidney failure	10 (20)	4 (17)	6 (23)
Chronic use of medications			
Non-steroidal anti-inflammatory drugs	5 (10)	1 (4)	4 (16)
ACE inhibitors	12 (24)	5 (20)	7 (28)
Systemic glucocorticoids	10 (20)	5 (20)	5 (20)

**Table2- Incidence rate of ARDS**

Study author	Region, country	Study type	Age(y)	No.of patients	No.of ARDS patients	No .of patient transferred to ICU	No.of death
Tzozos et al [23]	(Germany, USA, China, ITALY, South Korea)	Systematic review	18-70	2212	738/2212	429	347
Abohamr et al [32]	Saudi Arabia	Retrospective study	32-60	768	251/768	352	89
LI Liyang et al [2]	China	Systematic review	18-80	3375	1012/3375	342	21
Chand et al [17]	New York City/USA	Prospective study	18-70	300	275/300	300	157
Eastin et al [34]	WASHINGTON /USA	Retrospective study	43-92	21	12/21	12	11

## Conclusion

Incidence of acute lung injury among COVID19 patients is common, and a high rate of these cases tend to develop ARDS especially those who have preexisting

diseases and obesity. Furthermore, there are no significant differences regarding the rate of incidence between ARDS from other causes and COVID19 ARDS. Most of the studies included in this review are dependent on Berlin 2012 definition for ARDS as a diagnostic criterion. Elevation of inflammatory biomarkers is also



regarded as an indicator of ARDS incidence in more reviewed studies. Currently, there is no distinctive approach for management of this condition. Therefore, protective lung strategy, and other measurements suggested in typical ARDS are still considered to reduce acute lung injury development of ARDS, and worsening outcomes with COVID19 patients.

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