

Understanding Mortality Risk Among COVID-19 Vaccinated Individuals in the US: A Literature Review

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Background

- In the United States (US), COVID-19 vaccines have demonstrated remarkable efficacy in preventing deaths and severe illness, with safety profiles deemed acceptable by regulatory authorities and health experts. However, vaccine hesitancy persists due to concerns about adverse reactions, long-term effects, and perceived lack of trustworthy data among the general population and policymakers. Given the critical importance of vaccination in controlling the pandemic and the ongoing debate surrounding vaccine safety, there is a pressing need for comprehensive data on vaccine outcomes. Our study aims to address this gap by assessing COVID-19 mortality rates among vaccinated individuals in the US.

Methods

- Targeted literature searches were conducted by drafting a comprehensive search strategy to retrieve relevant data from published literature. MEDLINE[®] and Embase[®] databases were searched on 1st April 2024 to identify studies published from database inception until March 2024.

Results

- The database search identified 198 records. Following screening, 11 studies published as journal articles were included in this review (Figure 1).

Figure 1: Trial Flow of Studies Included in Literature Review

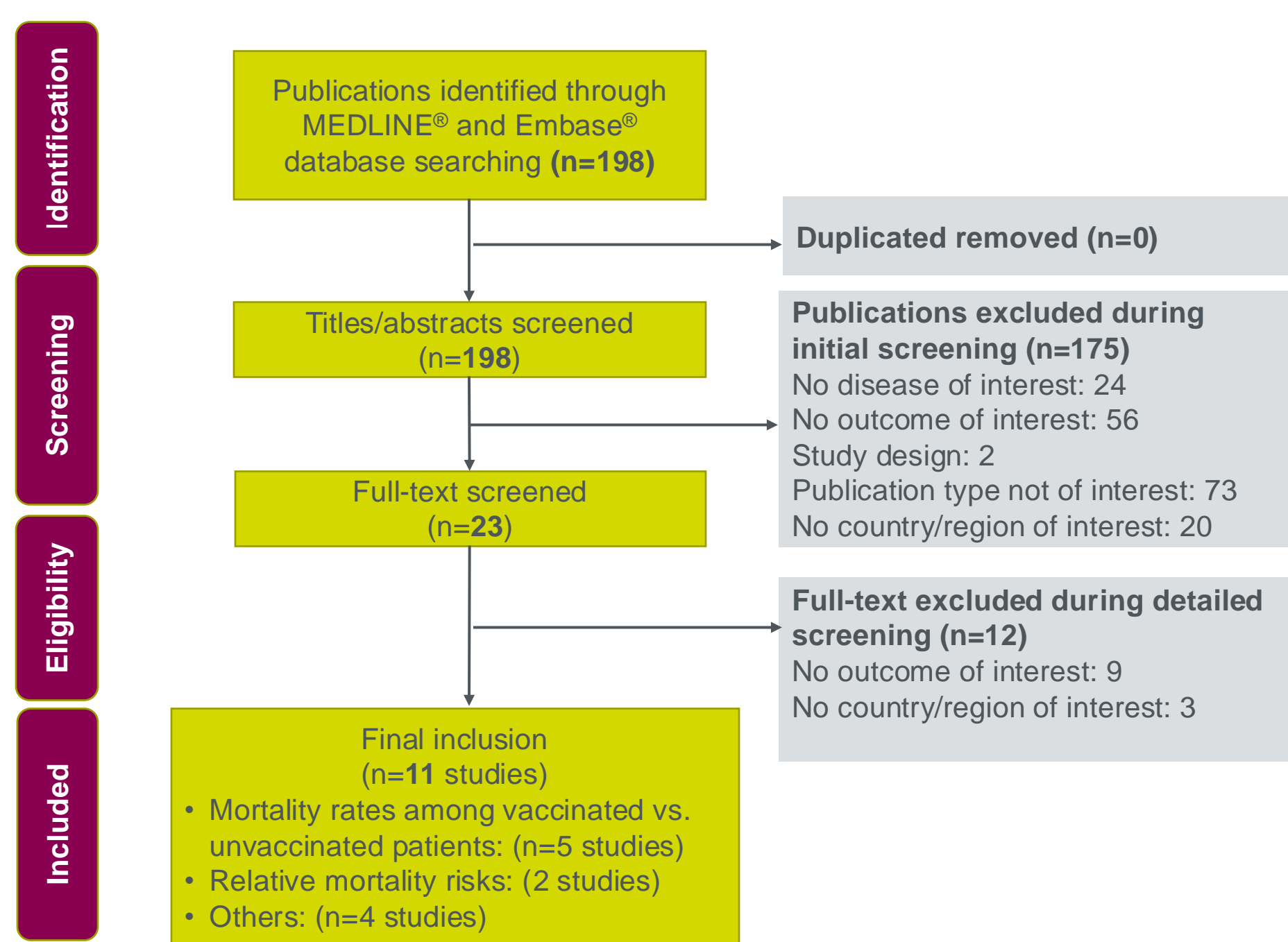
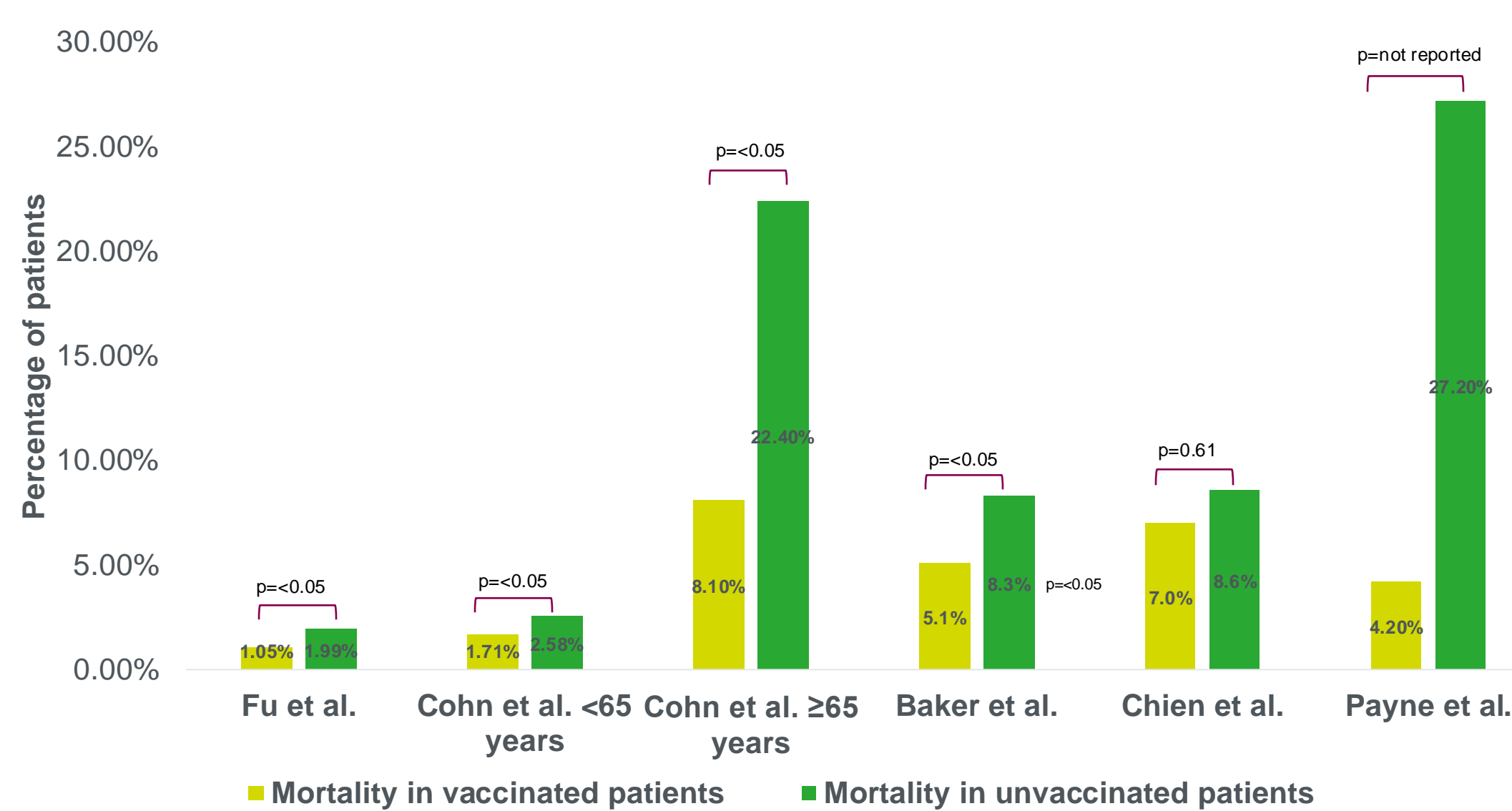


Figure 2: Mortality Rates Among Vaccinated Vs. Unvaccinated COVID-19 Patients



Conclusions

- Large database analyses conducted in overall US patients revealed that there were significantly lower COVID-19 related mortality rates in vaccinated individuals compared to unvaccinated individuals.
- Many studies consistently demonstrated that COVID-19 vaccination, substantially reduced mortality risk across diverse populations, including high-risk groups. Notably, Atanasov et al. reported zero deaths among triple-vaccinated individuals aged 18-59 years.
- While vaccination status is a crucial factor in COVID-19 outcomes, other variables such as age, comorbidities, and changes in virus variants over time can also influence mortality rates, highlighting the complexity of COVID-19 research and the need for comprehensive analysis.

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- Five studies provided direct comparison of COVID-19 mortality rates between vaccinated and unvaccinated patients (Figure 2, Table 1).

Table 1: COVID-19 Mortality Rates: Vaccinated vs. Unvaccinated

Study name	Region/State	Sample size	Study period	Data source	Gender (%female)	Age (year)	Type of vaccine	Patient population	Vaccinated patients (n)	Covid-19 mortality in vaccinated patients (%)	Unvaccinated patients (n)	Covid-19 mortality in unvaccinated patients (%)	P-value
Fu 2023	Across the US (74 sites)	10,412,853	11 December 2020 to 30 June 2022	National COVID Cohort Collaborative (N3C) database	57.4	18 to 30: 18.00% 30 to 50: 33.17% 50 to 65: 26.84% >65: 21.99%	Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen	Adults (≥18 years old)	2,491,556	1.05	7,921,297	1.99	<0.05
Cohn 2022	Across the US	780,225	1 February 2021 to 1 October 2021	Veterans Health Administration	14.4	<50: 23.77% 50 to 64: 28.58% ≥65: 47.65%	Pfizer-BioNTech, Moderna, Janssen	Adults (≥18 years old)	All ages: 498,148	<65 years: 1.71 ≥65 years: 8.10	All ages: 282,077	<65 years: 2.58 ≥65 years: 22.40	<0.05
Baker 2023	Across the US (21 healthcare systems)	86,732	1 January 2021 to 31 January 2022	The COVID EHR Cohort at the University of Wisconsin (CEC-UW)	52	Under 60 years: 44.7% 60-70 years: 22.6% Over 70 years: 32.7%	Pfizer, Moderna	Adult patients hospitalized with Covid-19	22,792	5.1 (95% CI, 4.8-5.4)	63,940	8.3 (95% CI, 8.1-8.5)	<0.05
Chien 2023	Texas	418	December 2020 to 31 October 2021	The University of Texas MD Anderson Cancer Center	39.5	Vaccinated: Median range: 67 (24-89) Unvaccinated: Median range: 56 (19-88)	Pfizer-BioNTech, Moderna, Johnson and Janssen	Patients with hematologic malignancies	243	7.0 (95% CI, 4.3-11.1)	175	8.6 (95% CI, 5.0-14.0)	0.61 (Not significant)
Payne 2023	Utah	2,072,908	18 December 2020 to 31 December 2021	Utah immunization registry	51.6	0-17: 13.20% 18-34: 28.20% 35-49: 22.72% 50-64: 18.39% ≥65: 17.49%	Not reported	Utah residents	NR	4.2	NR	27.2	NR

- Two studies conducted by Atanasov et al. (2023) provided data on vaccine effectiveness (VE) against death, and relative mortality risk (RMR = 1-VE) versus the unvaccinated (Table 2).

Table 2: Relative Mortality Risks by Time Period

Study name	Region	Sample size	Study period	Data source	Relative mortality risk for persons vaccinated with 2 doses, vs. the unvaccinated	Relative mortality risk for persons vaccinated with 3 doses, vs. the unvaccinated
Atanasov 2023 (a)					April-June 2021 (Alpha): 10.6% July-September 2021 (Delta, no boosters): 17.3% October-December 2021 (Delta, with booster): 21.1% January-June 2022 (Omicron): 36.2%	October-December 2021 (Delta, with booster): 7.7% January-June 2022 (Omicron): 11.0%
Atanasov 2023 (b)	Wisconsin (Milwaukee County)	722,000	1 April 2021 to 30 June 2022	Milwaukee County, Wisconsin	Age group: 18-59 years April-September 2021 (Moderna): 0.0% April-September 2021 (Pfizer): 12.1% October-December 2021 (Moderna): 4.9% October-December 2021 (Pfizer): 2.5% January-June 2022 (Moderna): 49.4% January-June 2022 (Pfizer): 43.6% Age group: 60+ years April-September 2021 (Moderna): 15.2% April-September 2021 (Pfizer): 34.9% October-December 2021 (Moderna): 18.4% October-December 2021 (Pfizer): 44.1% January-June 2022 (Moderna): 21.8% January-June 2022 (Pfizer): 55.6%	Age group: 18-59 years October-December 2021 (Moderna): 0.0% October-December 2021 (Pfizer): 0.0% January-June 2022 (Moderna): 0.0% January-June 2022 (Pfizer): 0.0% Age group: 60+ years October-December 2021 (Moderna): 13.4% October-December 2021 (Pfizer): 6.3% January-June 2022 (Moderna): 8.7% January-June 2022 (Pfizer): 13.1%

- Three studies examined mortality outcomes as summarized in Table 3. One compared mortality among a mixed population of unvaccinated/single-dose vs. double or triple vaccinated individuals. Another reported seroconversion and mortality outcomes after initial and booster vaccinations. The third presented mortality data of decedents with COVID-19-related mortality.

Table 3: Mortality Outcomes among different patient populations

Study name	Region/State	Sample size	Study period	Data source	Gender (%female)	Age (year)	Type of vaccine	Patient population	Mortality outcomes
O'Leary 2023	Across the US	12,936	25 December 2021 to 16 February 2022	Veteran Affairs Healthcare System	5.94	≥65: 67.6%	Pfizer-BioNTech, Moderna, Johnson and Johnson	Hospitalized patients with COVID-19 infection	• Overall, 14-day mortality rate: 4.35% • Mortality risk reduction compared to unvaccinated/single-dose: - Triple-vaccinated: 52% - Double-vaccinated: 39%
Ollila 2022	Rhode Island	378	February 2021 to February 2022	Rhode Island Hospital	49.7	Median (IQR): 69.7 (62.2-77.6)	Pfizer, Moderna, Johnson and Johnson	Patients with hematologic malignancies	• Among vaccinated patients (who received either initial or booster doses), COVID-19 infection occurred in 8.8%. Of those infected, mortality occurred in 0.8% (all of whom were seronegative)
Cavanaugh 2023	Kentucky	777	1 July 2021 to 13 August 2021	Kentucky Immunization Registry	45.8	20-29: 1.2% 30-39: 2.5% 40-49: 8.3% 50-59: 16.0% 60-69: 25.4% 70-79: 26.4% ≥80: 20.2%	Pfizer-BioNTech, Moderna, Janssen	Decedents with COVID-19-related mortality	• Total COVID-19 deaths: 777 • Vaccination status of deceased: - Unvaccinated: 76.2% - Partially vaccinated: 3.3% - Fully vaccinated: 20.5%

- In a remaining study conducted by Adhikari et al. (2024), among 152 adult patients admitted to Ohio State University hospital with acute respiratory failure, the COVID-19-related mortality rates were significantly higher for vaccinated patients compared to unvaccinated patients (p=0.002). However, this study had several limitations. During the study period, the virus changed, and the vaccination types were adjusted. Additionally, the types and combinations of comorbidities varied between both groups, which could contribute to the contrasting clinical outcomes.