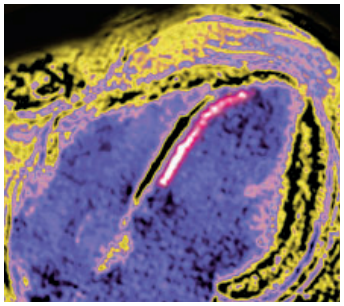
research

Predicting short term mortality in patients admitted to hospital with covid-19 p 101



Incidence of myocarditis and pericarditis after covid-19 mRNA vaccination p 102

Fever therapy and risk of death and adverse events p 104

ORIGINAL RESEARCH External validation and IPD meta-analysis

Clinical prediction models for mortality in patients with covid-19

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Study question Which prognostic models can accurately predict mortality in patients admitted to hospital with covid-19?

Methods Eight prognostic models, identified from a recent systematic review, were externally validated in 46 914 patients from 27 (clustered) cohorts across 18 countries. Individual participant data (IPD) were retrieved on patients admitted to hospital with polymerase chain reaction confirmed covid-19 from November 2019 to April 2021. A two stage IPD meta-analysis was performed to summarise the estimated models' C statistic, calibration slope, and observed to expected ratio across the clusters.

Study answer and limitations The 4C Mortality Score by Knight et al (pooled C statistic 0.80, 95% confidence interval 0.75 to 0.84, 95% prediction interval 0.72 to 0.86) and clinical model by Wang et al (0.77, 0.73 to 0.80, 0.63 to 0.87) had the highest discriminative ability. On average, 29% fewer deaths were observed than predicted by the 4C Mortality Score (pooled observed to expected ratio 0.71, 95% CI 0.45 to 1.11, 95% prediction interval 0.21 to 2.39), 35% fewer than predicted by the Wang clinical model (0.65, 0.52 to 0.82, 0.23 to 1.89) and 4% fewer than predicted by the Xie et al model (0.96, 0.59 to 1.55, 0.21 to 4.28). Although most of the models showed good discrimination, the predicted risk of mortality was too high. This could be because new covid-19 variants have emerged or treatments have improved since the development of these models.

What this study adds Although several models show promise for predicting short term mortality in patients admitted to hospital with covid-19, recalibration (intercept and slope updates) is needed before implementation in routine care.

Funding, competing interests, and data sharing See full paper on bmj.com for funding and competing interests. All code is available at github.com/VMTdeJong/COVID-19_Prognosis_IPDMA.

Models with best discrimination and calibration for predicting mortality in patients admitted to hospital with covid-19

Model	Model predictors	C statistic (95% CI)	Slope (95% CI)	Observed:expected ratio (95% CI)
4C Mortality Score	Age, sex, number of comorbidities (chronic neurological conditions and cardiac, respiratory, renal, liver, and connective tissue diseases, dementia, diabetes (type 1 and 2), AIDS/HIV, malignancy, obesity), respiratory rate, oxygen saturation (room air), Glasgow coma scale score, urea, C reactive protein	0.80 (0.75 to 0.84)	1.22 (0.92 to 1.52)	0.71 (0.45 to 1.11)
Wang clinical model	Age, history of hypertension, history of heart disease	0.77 (0.73 to 0.80)	0.50 (0.44 to 0.56)	0.65 (0.52 to 0.82)
Xie model	Age, lactate dehydrogenase, lymphocyte count, oxygen saturation	0.75 (0.68 to 0.80)	0.45 (0.27 to 0.63)	0.96 (0.59 to 1.55)

Myocarditis and pericarditis risk after covid-19 vaccination

ORIGINAL RESEARCH Living evidence syntheses and review

Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination

Pillay J, Gaudet L, Wingert A, et al

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Study question What are the incidence rates, risk factors, short term clinical course, and longer term outcomes of myocarditis and pericarditis after immunisation with covid-19 mRNA vaccines?

Methods Three databases and grey literature were searched (October 2020 to January 2022). Inclusion was targeted to large (>10 000 participants) or population based or multisite observational studies and surveillance data reporting on confirmed myocarditis or pericarditis (incidence and risk factors); case series (≥5; presentation, short outcomes, and longer term outcomes); and opinions, letters, reviews, and primary studies (mechanisms). Certainty of evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluation.

Study answer and limitations 46 studies were included. Incidence of myocarditis after mRNA covid-19 vaccination was highest in teenage boys (12-17 years, range 50-139 cases per million; low certainty) and young men (18-29 years, 28-147 per million; moderate certainty). For children aged 5-11 years and women aged 18-29 years, incidence with BNT162b2 (Pfizer-BioNTech) could be fewer than 20 cases per million (low certainty). For those aged 18-29 years, incidence of myocarditis is probably higher after vaccination with mRNA-1273 (Moderna) compared with BNT162b2 (moderate certainty). Among those aged 12-17, 18-29, and 18-39 years, incidence after the second mRNA vaccine dose might be lower when administered ≥31 days versus ≤30 days after the first dose (low certainty). Most cases (>90%) involved men aged 20-30 years, with onset two

COMMENTARY A weak evidence base leaves important questions unanswered

One of the main safety concerns associated with mRNA vaccines for covid-19 is the rare risk of myocarditis or pericarditis. The sheer number of published studies on this topic makes keeping up to date of the rapidly changing literature extremely challenging for clinicians.

In this context, Pillay and colleagues conducted a systematic review to examine incidence rates, risk factors, short term clinical course, and longer term outcomes of myocarditis and pericarditis after covid-19 mRNA vaccination. Among thousands of database citations through to 10 January 2022, their team ultimately focused on 46 studies.

First, their review provides evidence that the relative incidence of myocarditis is highest among young male individuals between the ages of 12 and 29 years after a second dose. Second, their study finds, with moderate certainty, that the incidence of myocarditis is probably higher after Moderna's mRNA vaccine than after Pfizer-BioNTech's vaccine. Third, with low certainty, they report that the risk of myocarditis or pericarditis might be lower when the second dose is administered more than 30 days after the first dose. Finally, the review finds that most patients are only briefly admitted to hospital and respond well to standard therapy, although long term follow-up is limited.

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Ongoing uncertainty

Despite the large numbers of studies reviewed, the overall certainty of the conclusions remains low, with a very wide range reported for myocarditis incidence. That we are now more than a year and a half into mass mRNA vaccination and still do not have strong certainty about the incidence of this clinically important outcome is disappointing. Because these events are rare, making precise estimates is difficult.

Additionally, ascertainment of the outcome or outcomes of interest differs from study to study, contributing to the uncertainty. Pillay and colleagues' research focused on studies of confirmed cases of myocarditis or pericarditis. The range of incidence estimates would be far wider if additional studies without such confirmation were included, but accuracy would suffer. Clearly, the incidence of myocarditis is rare after vaccination. Just how rare remains a question of major importance.

This living evidence syntheses and review finds that the incidence of myocarditis is probably higher after Moderna's vaccine than after Pfizer-BioNTech's vaccine. This finding has led multiple countries to prefer use of the Pfizer-BioNTech vaccine over the Moderna vaccine for young people.[6-8] US agencies have so far declined to make this recommendation. In a recent meeting of the vaccine advisory committee of the US Food and Drug Administration, the FDA

Uncertainties must be placed in the context of substantial and widely accepted benefits of vaccination

justified this position by use of its new data comparing risk between the two mRNA vaccines.[9] This study used International Classification of Diseases-10 codes to ascertain myocarditis and pericarditis with no case confirmation. Although Moderna vaccine recipients had an estimated excess risk of 28 myocarditis cases per million doses relative to Pfizer-BioNTech's vaccine, the 95% confidence interval spanned from 22 fewer cases to 77 more cases per million. The FDA concluded that insufficient evidence exists to confirm the higher risk, despite the international data reported in Pillay and colleagues' systematic review.

A paucity of data exists regarding longer term outcomes among patients with vaccine associated myocarditis. The Pillay review identified only 38 cases from studies with more than 90 days of follow-up. So how frequently electrocardiographic changes or symptoms, such as chest discomfort, can persist remains unclear. The CDC is surveying patients at least 90 days after vaccine associated myocarditis; preliminary data from 360 respondents interviewed after a median of 143 days from diagnosis were presented to the US Advisory Committee on Immunization Practices in February.[10] About a third of people still reported chest pain, although no control group was used

to four days after second dose and short (two to four days) stay in hospital. 16 mechanisms have been proposed. Data are limited for children, third vaccine doses, longer term outcomes, and pericarditis.

What this study adds Although low, the incidence of myocarditis is probably highest in young boys and men aged 12-29 years and is probably higher with the mRNA-1273 vaccine than BNT162b2 mRNA vaccine. Most cases are mild and self-limiting.

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No additional data available.

and response bias is likely. Roughly 80% (n=309) of 380 patients were judged by clinicians to have fully or probably fully recovered but more data and longer term follow-ups are urgently needed.

Although the data for myocarditis risk after a second dose is important, its future relevance is uncertain as the vaccination rollout moves to younger children. Many adolescents and young adults eligible for the adult primary series have already been vaccinated (in the US, at least), and now need information about the risks associated with booster doses. Recent studies suggest a non-negligible myocarditis risk after boosters,[11 12] and this issue will remain salient as boosters for young people are discussed again later this year.

In summary, a large body of reviewed studies continues to suggest that mRNA covid-19 vaccines are associated with a rare but heightened risk of acute myocarditis and pericarditis. These risks are highest in young men shortly after the second dose. Key uncertainties remain, including risks associated with boosters, risks associated with primary vaccination of young children, and the long term outcomes of those who experience myocarditis. But these uncertainties must be placed in the context of the substantial and widely accepted benefits of vaccination.

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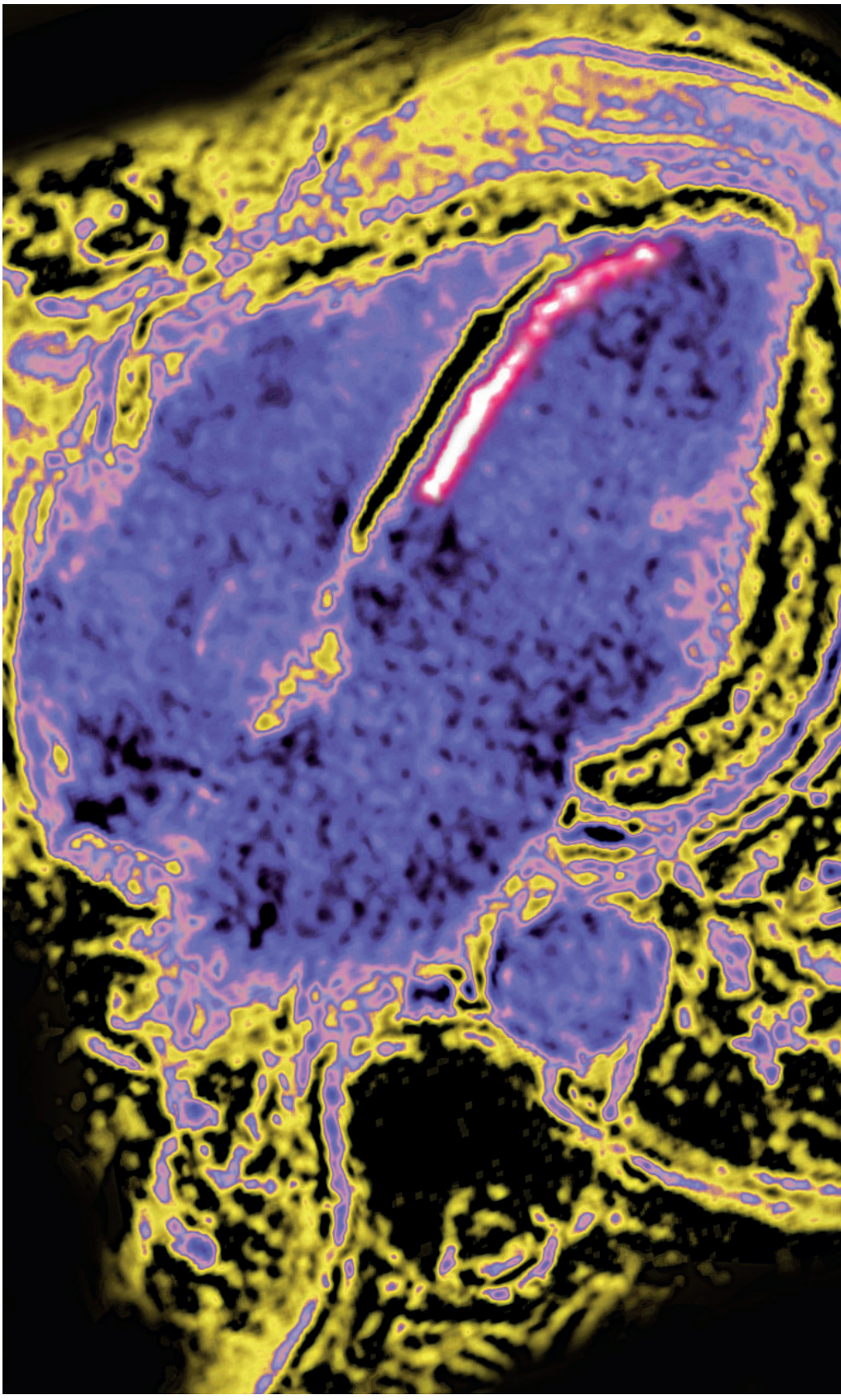

JAMES CAVALLINI/SPL

Fever therapy in febrile adults

Holgersson J, Ceric A, Sethi N, Nielsen N, Jakobsen JC

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Study question Does fever therapy affect the risk of death or serious adverse events compared with no fever therapy in febrile adults?

Methods This systematic review of the available evidence with meta-analyses and trial sequential analyses investigated whether fever therapy is beneficial in terms of mortality and serious adverse events. All relevant databases were searched to identify randomised clinical trials comparing any type of fever therapy with no fever therapy in adults diagnosed as having fever of any origin.

Study answer and limitations 42 trials assessing 5140 participants were included. All trials were assessed as being at high risk of bias. Meta-analysis and trial sequential analysis showed that the hypothesis that fever therapy reduces the risk of death (risk ratio 1.04, 95% confidence interval 0.90 to 1.19; I^2=0%; P=0.62; 16 trials; high certainty evidence) and the risk of serious adverse events (risk ratio 1.02, 0.89 to 1.17; I^2=0%; P=0.78; 16 trials; high certainty evidence) could be rejected. The smallest intervention effects that could be rejected using trial sequential analyses were 22% for mortality and 23% for serious adverse events.

What this study adds Fever therapy does not seem to affect the risk of mortality or serious adverse events. Inclusion of a wide population of febrile adults and a wide variety of fever therapies achieved an information size allowing the hypothesis that fever therapy reduces the risk of death and serious adverse events to be rejected.

Funding, competing interests, and data sharing
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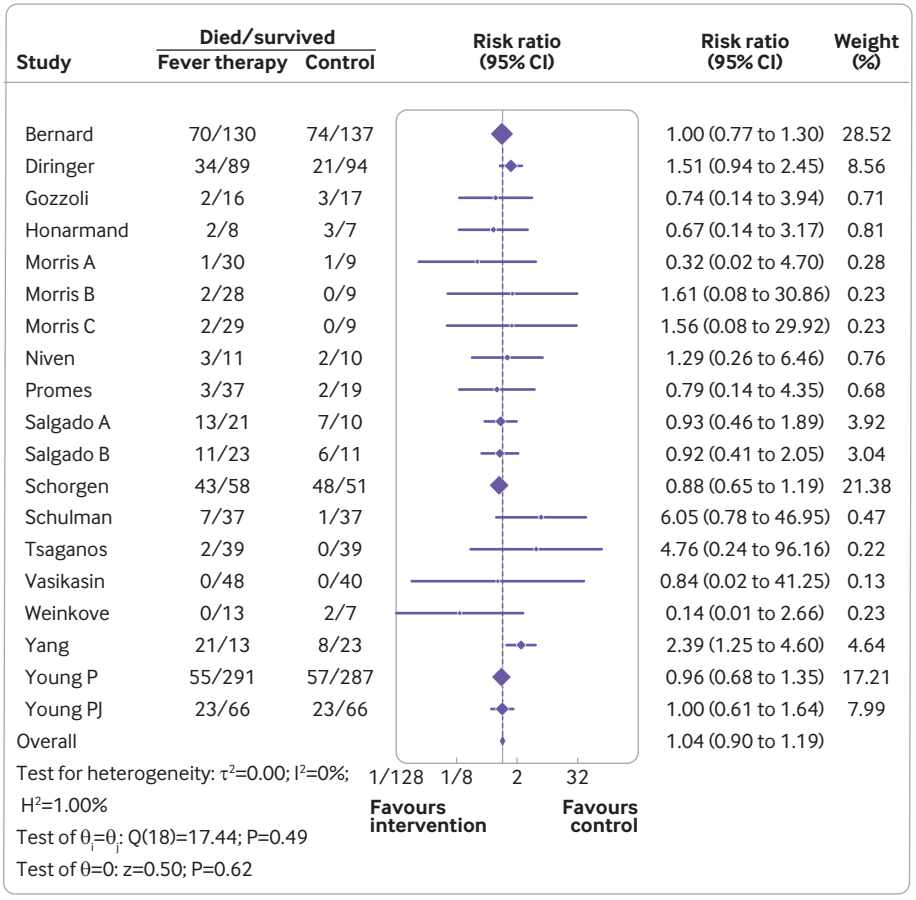

Random effects meta-analysis comparing fever therapy versus control interventions for all cause mortality