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Prognostic factors for mortality in patients infected with New World hantaviruses: a systematic review and meta-analysis

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ABSTRACT

Introduction One of the challenges in managing patients with hantavirus infection is accurately identifying individuals who are at risk of developing severe disease. Prompt identification of these patients can facilitate critical decisions, such as early referral to an intensive care unit. The identified prognostic factors could be of utility in guiding medical care to enhance the management of hantavirus infection.

Objective To identify and evaluate prognostic factors associated with mortality in hantavirus infection.

Methods We conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-reported systematic review following Cochrane guidance adapted for prognosis. We searched PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Biblioteca Virtual de Saúde or Lilac and EMBASE, from 1 January 1993 to 2 October 2025. We included studies evaluating individual prognostic factors or risk assessment models of New World hantavirus infections, with no restrictions on study design, publication status or language. When feasible, we conducted meta-analyses for prognostic factors using the inverse variance-based method with random effect model. We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results We included 25 studies with a total of 7284 participants. We identified the following prognostic factors for which we found moderate to high certainty that are associated with increased mortality: age over 18 years, female sex, rural residence, elevated creatinine levels, increased haematocrit, signs of bleeding and the presence of infiltrates on chest radiographs.

Discussion Our systematic review identified prognostic factors for mortality in patients with New World hantavirus infection. These factors can inform clinicians in making more informed management decisions. Furthermore, our findings lay the groundwork for the future development of a clinical prognostic model, potentially enhancing patient care and outcomes.

PROSPERO registration number CRD42021225823.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We rated certainty using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic factors and reported both relative effects and prevalence-adjusted absolute risk differences (anchored to overall mortality risk) to support clinical use.
⇒ We used a prespecified analytic framework with a comprehensive multidatabase search; meta-analysis when feasible; priority to adjusted estimates; pre-specified sensitivity analyses (adjusted-only, excluding high-risk-of-bias studies, excluding suspected cohort overlap); and subgroups by viral species.
⇒ Predominance of unadjusted estimates and sparse reporting of key confounders (eg, comorbidities, baseline severity) constrained confounder control and some subgroup analyses.

INTRODUCTION

Hantaviruses, members of the *Hantaviridae* family, genus *Orthohantavirus,* are single-stranded RNA viruses characterised by their spherical shape, typically measuring 80–100 nm in size.[1] Unlike other viruses in the *Hantaviridae* family, viruses belonging to the *Orthohantavirus* genus do not rely on arthropods as vectors; instead, they are primarily hosted by rodents and certain small mammals. Each hantavirus genotype tends to associate with specific rodent species. These rodents typically maintain chronic infections with high rates of viral replication, often remaining asymptomatic. Rodent populations fluctuate based on environmental factors such as climate and food availability, with increases in rodent density sometimes correlating with an uptick in human cases.[2] There are two groups of hantaviruses that differ in their clinical presentations: Old World hantaviruses are predominant in Asia and Europe and produce a condition known as haemorrhagic fever with renal syndrome (HFRS), and New World hantaviruses, including the Andes virus (ANDV), Sin Nombre virus (SNV), Laguna Negra virus (LANV), Juquitiba virus (JUQV)

and Araucaria virus (ARAV), predominate in America and can cause hantavirus pulmonary syndrome (HPS) in humans, a severe respiratory disease characterised by rapid onset of symptoms and high mortality rates. HPS begins with nonspecific influenza-like symptoms and can progress quickly to severe respiratory distress and cardiogenic shock, often requiring intensive care and mechanical ventilation. The mortality rate for HPS can be as high as 35%–50%, making early identification and management of prognostic factors crucial for improving patient outcomes.[3–5]

Prognostic factors, whether used alone or combined in risk assessment models, provide a means of stratifying patients with hantavirus infection based on their risk of developing severe disease or mortality.

This stratification can inform optimised treatment strategies and resource allocations. Early identification of patients at risk of deterioration, progression to severe forms of the disease or higher mortality rates enables prompt initiation of treatment, monitoring and appropriate support, including timely referrals to specialised intensive care units experienced in managing severe HPS patients and venoarterial extracorporeal membrane oxygenation.[6–8]

Although some prognostic factors have been proposed and are frequently considered by clinicians caring for patients with hantavirus infections, these factors are not based on a systematically structured assessment of the evidence. Furthermore, no validated prognostic models are currently available to guide the management of patients with hantavirus infection.[9]

This systematic review and meta-analysis aims to provide for the first time a comprehensive summary of the available evidence on prognostic factors for mortality in hantavirus infection caused by New World hantaviruses.

METHODS

Our review adheres to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' 2020 for reporting guidelines[10] (online supplemental table S52). We followed Cochrane guidance adapted for prognosis reviews (drawing on the Cochrane Handbook and the Cochrane Prognosis Methods Group's methods) for question formulation, searching, study selection, data extraction and synthesis.[11–13] Data items for prognostic factor studies were extracted using the CHARMS-PF (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies – Prognostic Factors) checklist.[14] The protocol for this systematic review was registered in the international prospective register of systematic reviews PROSPERO (Registration number: CRD42021225823).[15] See amendments to the original protocol in online supplemental S3 file.

Search strategies

We performed highly sensitive searches in MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), *Biblioteca Virtual de Saúde* (BVS) or Lilacs and EMBASE, from 1 January 1993 to 2 October 2025. The search strategy included keywords related to prognostic factors for mortality on New World hantaviruses. No restrictions regarding study design, publication status or language were applied. Detailed search strategies can be consulted in online supplemental S1 file. We also reviewed the reference lists of each included study and conducted cross-referencing in Google Scholar using each included study as the index reference.

Study selection

Four reviewers worked independently and in duplicate to perform study selection, which involved screening titles and abstracts as well as potentially eligible full-text articles. Disagreements were resolved through discussion. We included studies that examined individual prognostic factors or risk assessment models for patients with hantavirus infections, based on the typologies of prognosis proposed by Iorio and colleagues and the PROGnosis RESearch Strategy Group framework, without applying any restrictions based on analytical methods.[16] Excluded studies: (1) Old World orthohantaviruses causing HFRS; (2) New World case reports/series with fewer than five participants and (3) studies without mortality outcomes or extractable mortality data.

Outcomes

We prespecified all-cause in-hospital mortality during the index admission (reflecting deaths directly attributable to hantavirus infection) as the sole outcome for quantitative synthesis; when in-hospital status was unavailable, we accepted all-cause 28–30-day mortality as a proximate substitute.

Prespecified candidate prognostic factors and rationale

For transparency, we prespecified candidate prognostic factors aligned with routine bedside practice and prior biological plausibility across demographic, clinical, laboratory and radiological domains, and we also included any routinely used bedside variables reported as candidate factors in one or more studies.

Data extraction

For each eligible study, two pairs of reviewers independently extracted key information: the year of publication, country and study period for study characteristics; sample size, context and demographic details for population characteristics; definitions and details of candidate prognostic factors; and measures of association or crude event rates for each candidate prognostic factor. We additionally recorded study centre(s), enrolment dates to assess possible cohort overlap across reports.

Data synthesis and analysis

We presented the findings of individual prognostic factors both in tabular and narrative formats. To enhance comparability and accuracy, we standardised the units of measurement for each prognostic factor and ensured

consistency in the direction of predictors.[17] Whenever feasible, when two or more studies were available, we conducted meta-analyses for candidate prognostic factors and their association with the selected outcomes. To generate an overall measure of association, we used the generic inverse variance method. We employed random-effects models based on the DerSimonian-Laird method, using the metafor package in R software.[18]

For each candidate prognostic factor, we present the measure of association as ORs along with their corresponding 95% CIs. In studies that reported the measure of association as a HR or risk ratio, we converted them to ORs using the outcome prevalence reported in the studies.[19 20] When measures of association were not provided for dichotomous variables, we used the crude event rate to calculate ORs. Information on continuous variables without measures of association was excluded. Additionally, we calculated absolute risk differences (ARDs) attributable to each individual candidate prognostic factor by applying the pooled ORs to estimated baseline risks (see 'Baseline risks' below).

Assessment of certainty of evidence

Assessment of the certainty of evidence (CoE) was conducted for each candidate prognostic factor using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[21] The main concerns were between-study heterogeneity, addressed under the inconsistency domain, and lack of adjustment for confounding, considered within the risk-of-bias (RoB) domain. Two reviewers independently assessed the RoB of individual included studies using the Quality in Prognosis Studies (QUIPS)[17 18] tool for prognostic factor studies, which considered population characteristics, attrition, prognostic factor and outcome measurement, and potential residual confounding. For the study-level confounding domain, we judged multivariable models as adequately adjusted when they included at least one indicator of disease severity. We categorised each study as low, some concerns or high RoB. We defined low RoB as standardised baseline factor measurement, appropriate outcome ascertainment and adjusted analyses that controlled for age and at least one severity indicator. We assigned 'some concerns' RoB to retrospective designs with otherwise appropriate measurement and ascertainment and adequate control of confounding but minor design or execution limitations. We assigned high RoB when studies showed insufficient control of confounding or important shortcomings in measurement or follow-up. Within the GRADE assessment, we downgraded according to these categories. When low or some-concerns RoB studies drove the pooled estimates, we did not downgrade. When estimates relied mainly on high-RoB studies, or when sensitivity analyses that excluded high-RoB studies materially changed the effect, we downgraded one level for RoB. Full operational details of the certainty of evidence (CoE) assessment are provided in online supplemental S2 file (Certainty of the evidence assessment).

Result interpretation

To facilitate the interpretation and clinical application of identified prognostic variables, our research team set an arbitrary threshold of a 2% absolute risk increase or decrease, defining a clinically significant escalation in mortality risk. This threshold was established to differentiate between negligible and meaningful changes in risk, aiding clinicians and researchers in assessing the practical importance of each prognostic factor. This approach allows for a clearer understanding of when changes in prognostic indicators become significant enough to influence clinical decisions and public health interventions.

Baseline risks

For each candidate prognostic factor, we estimated a baseline risk (risk in the absence of that factor). We defined the overall mortality risk as the median mortality across included studies (34%). We expressed baseline risks as percentages using this overall mortality risk, the prevalence of each factor and the corresponding estimates of association.[22]

Additional analysis

We performed sensitivity analyses for all factors excluding studies at high RoB, retaining those at some concerns/low (restricting to adjusted estimates); these prespecified analyses were compared with the primary results to assess robustness. If adjusted effects remained consistent under these restrictions, we retained the global estimate and did not downgrade certainty for RoB; if estimates were discordant, we prioritised the some concerns/low–RoB estimate for reporting; and when adjusted evidence was too sparse to carry sufficient weight, we reported the global estimate and downgraded certainty accordingly.

We also performed prespecified subgroup analyses by New World hantavirus species to assess effect modification, for example, whether the association between each candidate prognostic factor and mortality differed by species. Where data allowed, we reported species-specific estimates alongside the pooled effect. Finally, we conducted a sensitivity analysis excluding studies with a high probability of including overlapping cohorts of patients to assess whether the effect estimates were substantially modified following their exclusion.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

We initially identified 5329 records through databases. After removing 3214 duplicates, we reviewed 2115 articles by title and abstract. After full-text assessment, we included 25 primary studies[23–47] in the review, as detailed

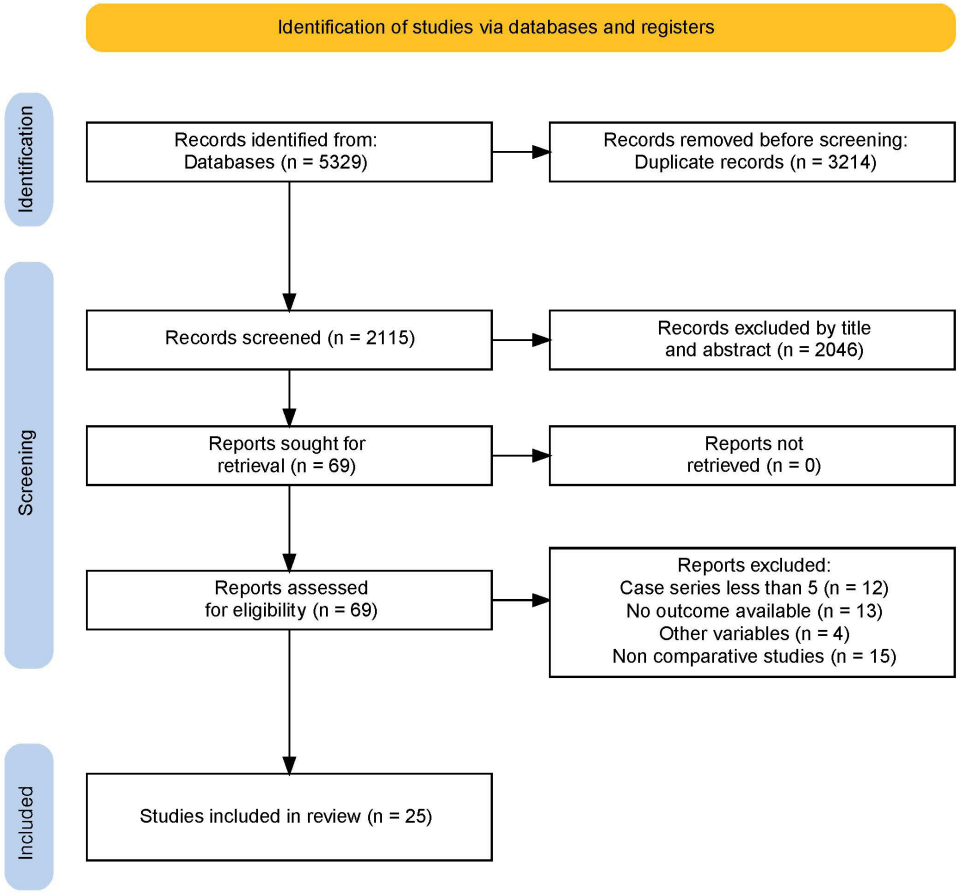

Figure 1 Identification of studies via databases and registers. Records identified through database searching (n=5329). After removal of duplicates (n=3214), 2115 records remained for title/abstract screening, of which 2046 were excluded. 69 full-text reports were assessed for eligibility (none were not retrieved). Full-text articles excluded (n=44) with reasons: case series with fewer than five patients (n=12), outcome not reported (n=13), non-relevant variables (n=4) and non-comparative designs (n=15). 25 studies were included in the review.

in figure 1. Excluded full-text reports with reasons are listed in online supplemental table S2.

The studies were conducted across several countries, including Argentina, Brazil, Canada, Chile and the USA, spanning cohort periods from 1993 to 2025. The viral species studied included ANDV in 13 studies with a total of 3159 participants, SNV in 5 studies with a total of 1436 participants, JUQV, ARAV and LANV in 4 studies with a total of 2592 participants. Diagnostic methods varied and included ELISA IgM/IgG, reverse transcription PCR, recombinant immunoblot assay and immunohistochemistry. For more detailed information about the studies, see table 1.

Across the 25 included studies, data were available for 17 candidate prognostic factors.

RoB of included studies

All included studies were retrospective (cohort, case series or case–control) and none was judged at overall low RoB; only eight studies reported adjusted estimates for at least one candidate factor and were classified as some concerns,[25 26 30–32 37 40 47] with the remainder at high RoB (table 2).

Prognostic factors for mortality in hantavirus infection

We present the assessed candidate prognostic factors organised into different categories to facilitate their understanding and analysis. A summary of the assessment of all candidate prognostic factors is presented in table 3.

Factors related to general patient characteristics

Age greater than 18 years

This factor was assessed in 11 studies[23 26 28–30 32 33 36 37 44 45] including 4812 participants. Definitions were heterogeneous, with cut-offs at >18 and >20 years. Age >18 years is not a prognostic factor for mortality (OR 1.03; 95% CI 0.89 to 1.18), with an ARD 0.7% higher (95% CI from 0.2% lower to 1.2% higher) and high certainty (⊕⊕⊕⊕) (figure 2).

Female sex

This factor was evaluated in 19 studies[23 24 26 28–33 35–37 42–48] including 5826 participants. Female sex is a prognostic factor for mortality (OR 1.37; 95% CI 1.20 to 1.57), with an ARD 5.9% higher (95% CI from 2.8 to 8.8 higher) and high certainty (⊕⊕⊕⊕) (figure 3).

Table 1 Characteristics of included studies

First author	Year	Country (cohort years)	N	Study design	Age (central tendency)	Deaths (n)	Diagnostic method	Viral species (variant)
Wernly[23]	2011	USA (1994–2010)	51	Retrospective cohort	Mean 39.6 y (SD 15.4)	17	RIBA, ELISA IgM/IgG	SNV
Warner[24]	2020	Canada (1989–2019)	143	Retrospective cohort	Mean 42 y (SD 15), range 7–76	34	IgM, IgG seroconversion, RT-PCR	SNV
Vial[25]	2019	Chile (2004–2013)	139	Retrospective cohort, adjusted estimates	Mean 37 y (SD 14.8), range 10–77	12	ELISA, RT-qPCR	ANDV
Tortosa[26]	2022	Argentina (1996–2022)	123	Retrospective cohort, adjusted estimates	Mean 35 y (SD 17.1)	50	IgM (two samples) and RT-PCR	ANDV
Riquelme[27]	2015	Chile (1995–2012)	103	Retrospective cohort	Mean 35.7 y (SD 16)	33	RT-PCR	ANDV
Ramos[28]	2001	USA (1993–2000)	13	Retrospective cohort	Median 14 y (range 10–16)	4	IgM/IgG	SNV
Pantozzi[29]	2011	Argentina (1996–2009)	291	Retrospective cohort	Median 28 y (range 15–49)	79	ELISA IgM, RT-PCR	ANDV (Lechiguanas, Buenos Aires, Plata)
Oliveira[30]	2016	Brazil (1999–2011)	251	Retrospective cohort, adjusted estimates	Mean 34.56 y (SD 13.38)	73	ELISA IgM, RT-PCR	Juquitiba virus
Menezes[31]	2016	Brazil (2007–2013)	73	Retrospective cohort, adjusted estimates	Mean 34.9 y (SD 13.8)	42	ELISA IgM	NR
Maleki[32]	2019	Argentina (2010–2016)	93	Retrospective cohort, adjusted estimates	Mean 36 y (SD 16)	34	ELISA IgM, RT-PCR	ANDV
MacNeil[33]	2011	USA (1993–2009)	510	Retrospective cohort	Median 38 y (IQR 20–50)	178	IgG, PCR	SNV
López[34]	2021	Chile (2001–2018)	175	Retrospective cohort	Median 35 y (IQR 23–46)	4	ELISA IgM, RT-PCR	ANDV
Limongi[35]	2007	Brazil (1998–2005)	23	Retrospective cohort	Median 23 y (SD 13.6)	5	ELISA IgM, RT-PCR	NR
Iglesias[36]	2016	Argentina (2009–2014)	86	Retrospective cohort	Median 35 y (IQR 14–21)	22	ELISA IgM, RT-PCR	ANDV (Buenos Aires, Plata, Lechiguanas)
Fonseca[37]	2020	Brazil (2007–2015)	1004	Case control, adjusted estimates	98%>10 y	410	ELISA IgM, RT-PCR	Juquitiba virus, ARAV, Anajatuba, Castelo, LANV
Da Rosa Elkhoury[38]	2012	Brazil (1993–2006)	855	Retrospective cohort, adjusted estimates	Mean 33 y (IQR 20–39)	336	ELISA IgM/IgG	Juquitiba virus, ARAV (Castelo, Anajatuba)
Castillo[39]	2001	Chile (1997–1999)	13	Retrospective cohort	Mean 30 y (range 19–45)	7	ELISA IgM/IgG	ANDV
Arita[40]	2019	Brazil (1992–2016)	280	Retrospective cohort, adjusted estimates	NR	107	NR	ANDV
Ferres[48]	2010	Chile (1997–2007)	24	Retrospective cohort	<13 y (children)	7	ELISA IgM, RT-PCR	ANDV
Santana[42]	2006	Brazil (1993–2004)	27	Retrospective cohort	NR	13	ELISA IgM, RT-PCR	NR
Rodríguez[46]	2023	Argentina (1997–2021)	583	Retrospective cohort	NR	132	ELISA IgM, RT-PCR	ANDV (Buenos Aires, Plata, Lechiguanas)
Thorp[44]	2023	USA (1993–2018)	719	Case series	Median 38 y (IQR 26–51)	253	RT-PCR, ELISA IgM/IgG	SNV

Continued

Table 1 Continued

First author	Year	Country (cohort years)	N	Study design	Age (central tendency)	Deaths (n)	Diagnostic method	Viral species (variant)
Martinez[43]	2010	Argentina (1995–2008)	710	Retrospective cohort	Mean 30 y	183	ELISA IgM, RT-PCR	ANDV
Alonso[45]	2019	Argentina (2009–2017)	533	Retrospective cohort	Mean 32.5 y (range 0–86)	114	ELISA IgM/IgG, RT-PCR	ANDV (Orán, Bermejo, Buenos Aires, Lechiguanas, Plata, South)
Willemann[47]	2014	Brazil (2007–2010)	462	Case control, adjusted estimates	Mean 33.5 y (SD 13.7)	166	ELISA IgM, RT-PCR	Juquitiba virus, ARAV (Anajatuba, Castelo), LANV[3]

ANDV, Andes virus; ARAV, Araucaria virus; LANV, Laguna Negra virus; NR, not reported; RIBA, recombinant immunoblot assay; RT-PCR, reverse transcription PCR; SNV, Sin Nombre virus; y, years.

Obesity

Only one study[23] assessed obesity as a candidate prognostic factor (n=51). In that study, overweight/obesity was defined as weight >80 kg. It is uncertain whether obesity is a prognostic factor for mortality (OR 2.47 95% CI 0.73 to 8.36), with an ARD 18.8% higher (95% CI from 6.6 lower to 31.5 higher) and very low certainty (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB (online supplemental figure S3).

Rural residence

This factor was evaluated in 4 studies[30 31 37 47] including 1585 participants. We use the pooled estimates from the two studies[37 47] judged as 'some concerns' in the RoB assessment (see Additional analyses). Residence in rural areas (vs urban) is probably a prognostic factor for mortality (OR 1.60; 95% CI 1.14 to 2.24), with an ARD 10.3% higher (95% CI from 3.1% to 16.1% higher) and moderate certainty (⊕⊕⊕⊖). We downgraded one level of certainty for imprecision (figure 4).

Factors related to clinical presentation

More than 7 days from the onset of symptoms

This factor was evaluated in 3 studies[29 35 40] including 1154 participants. A delay of more than seven days from symptom onset to first consultation was used as the exposure, with slight variations in the cutoff across studies (6–8 days). It is uncertain whether a delay of more than seven days from the onset of symptoms is a prognostic factor for mortality (OR 0.74; 95% CI 0.46 to 1.17), with ARD 7.4% lower (95% CI from 18.5% lower to 3.9% higher) and very low certainty (⊕⊖⊖⊖). We downgraded two levels of certainty for very serious imprecision and one level for RoB (online supplemental figure S4).

Headache

This factor was evaluated in 3 studies[30 31 47] including 490 participants. The presence of headache as a presenting symptom may be a prognostic factor for mortality (OR 0.54; 95% CI 0.30 to 0.96), with an ARD 19.0% lower (95% CI from 1.0% lower to 46.9% lower) and low certainty (⊕⊕⊖⊖). We downgraded one level of certainty for imprecision and one level for RoB (online supplemental figure S5).

Abdominal pain or diarrhoea

This factor was evaluated in 2 studies[30 31] including 316 participants. It is uncertain whether the presence of abdominal pain as a presenting symptom is a prognostic factor for mortality (OR 1.20; 95% CI 0.73 to 1.96), with an ARD 4.3% higher (95% CI from 8.4% lower to 13.7% higher) and very low certainty. (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB (online supplemental figure S9).

Vomits

This factor was evaluated in 2 studies[30 31] including 317 participants. It is uncertain whether the presence of vomiting as a presenting symptom is a prognostic factor for mortality (OR 1.18; 95% CI 0.68 to 2.06), with an ARD 3.9% higher (95% CI from 10.9% lower to 13.7% higher) and very low certainty (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB (online supplemental figure S8).

Signs of bleeding in the skin or mucous

This factor was evaluated in five studies[27 30 31 38 40] including 1561 participants. Signs of bleeding were defined as follows: in one study,[27] as haemorrhagic manifestations—haematuria, cutaneous or puncture-site bleeding, haemoptysis, metrorrhagia, epistaxis, gingival bleeding, rectorrhagia and post-lumbar puncture epidural haematoma—and in the other studies,[30 31 38 40] as petechiae or unspecified haemorrhagic phenomena. Signs of bleeding are probably a prognostic factor for mortality (OR 2.06; 95% CI 1.02 to 4.27), with an ARD 16.3% higher (95% CI from 0% to 27.9% higher) and moderate certainty (⊕⊕⊕⊖). We downgraded one level of certainty for imprecision (online supplemental figure S34).

Radiological findings

Infiltrates observed in all four quadrants on chest radiograph

This factor was evaluated in 5 studies[27 30 38 40 47] including 1869 participants. Diffuse pulmonary infiltrates on chest

Table 2 Risk of bias of included studies (QUIPS tool)

Author	Study participation	Study attrition summary	Prognostic factor measurement	Outcome measurement summary	Study confounding summary	Statistical analysis and presentation summary	Overall risk of bias
Wernly *et al*[23] (2011)	Low	Some concerns	High	Low	High	Low	High
Warner *et al*[24] (2020)	Low	Low	High	Low	High	Low	High
Vial *et al*[25] (2019)	Low	Low	High	Low	Low	Low	Some concerns
Tortosa *et al*[26] (2022)	Low	Low	High	Low	Low	Low	Some concerns
Riquelme *et al*[27] (2015)	Low	Low	High	Low	High	Low	High
Ramos *et al*[28] (2001)	Low	Some concerns	High	Low	High	Some concerns	High
Pantozzi *et al*[29] (2011)	Low	Low	High	High	High	Some concerns	High
Oliveira *et al*[30] (2016)	Low	Low	High	Low	Low	Low	Some concerns
Filho *et al*[31] (2016)	Low	Low	High	Low	Low	Low	Some concerns
Maleki *et al*[32] (2019)	Low	Low	High	Low	Low	Low	Some concerns
MacNeil[33] (2011)	Low	Low	High	Low	High	Low	High
López *et al*[34] (2021)	Low	Low	High	Low	High	Low	High
Limongi *et al*[35] (2007)	Low	Low	High	Low	High	Low	High
Iglesias *et al*[36] (2016)	Low	Low	High	Low	High	Low	High
Fonseca *et al*[37] (2020)	Low	Low	High	Low	Low	Low	Some concerns
da Rosa Elkhoury *et al*[38] (2012)	Low	Low	High	Low	High	Low	High
Castillo *et al*[39] (2001)	Low	Low	High	Low	High	Low	High
Arita and Shimakura[40] (2019)	Low	Low	High	Low	Low	Low	Some concerns
Ferrés *et al*[41] (2010)	Low	Low	High	Low	High	Low	High
Santana *et al*[42] (2006)	Low	Low	High	Some concerns	High	Some concerns	High
Rodríguez *et al*[46] (2023)	Low	Low	High	Low	High	Low	High
Thorp *et al*[44] (2023)	Low	Low	High	Low	High	Low	High
Martinez *et al*[43] (2010)	Low	Low	High	Low	High	Low	High
Alonso *et al*[45] (2019)	Low	Low	High	Low	High	Low	High
Willemann and de Oliveira[47] (2014)	Low	Low	High	Low	Low	Low	Some concerns

QUIPS, Quality in Prognosis Studies.

radiography were variously defined as: infiltrates on admission chest X-ray, bilateral interstitial infiltrates, diffuse infiltrates without quadrant specification, and unspecified radiologic criteria in two studies. Diffuse pulmonary infiltrates are probably a prognostic factor for mortality (OR 5.18; 95% CI 2.15 to 12.52), with an ARD 25.5% higher (95% CI from 15.5% to 30% higher) and moderate certainty (⊕⊕⊕⊖). We downgraded one level of certainty for inconsistency (figure 5).

Laboratory factors (measured in blood or plasma)

Increased haematocrit

This factor was evaluated in 9 studies[26 30–33 38–40 47] including 2158 participants. Elevated haematocrit was variably defined, with thresholds ranging from >42% to >50%. Elevated haematocrit is a prognostic factor for mortality (OR 1.92, 95% CI 1.43 to 2.58), with an ARD 13.4% higher (95% CI from 9.3% to 16.8% higher) and high certainty (⊕⊕⊕⊕) (figure 6).

Table 3 Summary of findings table

Prognostic factor	Number of studies	Number of participants	OR (95% CI)	Prevalence of the factor studied in the population (%)	Risk difference with PF (%)	Overall certainty	Summary of the candidate prognostic factor
Factors related to general patient characteristics							
Age (>18 years)	11[23 26 28–30 32 33 36 37 44 45]	4812	1.03 (0.89 to 1.18)	88%	0.2% more (from 0.7% less to 1.2% more)	**High*** *⊕⊕⊕⊕	Age >18 years is not a prognostic factor.
Female sex	19[23 24 26 28–33 35–37 42–48]	5826	1.37 (1.20 to 1.57)	25%	5.9% more (from 2.8% to 8.8% more)	**High*** ⊕⊕⊕⊕	Female sex is a prognostic factor.
Rural residence	4[30 31 37 47]	1585	1.60 (1.14 to 2.24)	51%	10% more (from 3.1% to 16.1% more)	**Moderate†** ⊕⊕⊕⊖	Rural (vs urban) residence is probably a prognostic factor.
Obesity	1[23]	51	2.47 (0.73 to 8.36)	54%	18.8% more (from 6.6% less to 31.5% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether obesity is a prognostic factor.
Factors related to clinical presentation							
>7 days from symptom onset	3[26 32 37]	1154	0.74 (0.46 to 1.17)	11.6%	7.4% less (from 18.5% less to 3.9% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether >7 days since symptom onset is a prognostic factor.
Signs of bleeding	5[27 30 31 38 40]	1561	2.07 (1.02 to 4.2.7)	24%	16.3% more (from 0% more to 27.9% more)	**Moderate¶*** ⊕⊕⊕⊖	The presence of bleeding signs is probably a prognostic factor.
Vomiting	2[30 31]	317	1.18 (0.68 to 2.06)	72.5%	3.9% more (from 10.9% less to 13.7% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether vomiting is a prognostic factor.
Abdominal pain	2[30 31]	316	1.20 (0.73 to 1.96)	57.4%	4.3% more (from 8.4% less to 13.7% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether abdominal pain is a prognostic factor.
Headache	3[30 31 47]	490	0.54 (0.3 to 0.96)	82%	19.4% less (from 46% less to 1% less)	**Low‡§** ⊕⊕⊖⊖	Headache may be a prognostic factor.
Laboratory factors (measured in blood, plasma or urine)							
Increased haematocrit	9[26 30–33 38–40 47]	2158	1.92 (1.43 to 2.58)	55%	13.4% more (from 9.3% more to 16.8% more)	**High*** ⊕⊕⊕⊕	Increased haematocrit is a prognostic factor.
Thrombocytopenia	8[23 26 30–33 39 47]	1117	1.44 (0.82 to 2.60)	73%	7.7% more (from 5.3% less to 16.2% more)	**Low‡**** ⊕⊕⊖⊖	A decreased platelet count may be a prognostic factor.
Elevated serum creatinine	6[26 27 30 33 39 42]	679	2.52 (1.47 to 4.34)	41.1%	18.5% more (from 9% more to 25.2% more)	**Moderate§** ⊕⊕⊕⊖	Increased plasma creatinine is probably a prognostic factor.
Proteinuria	1[34]	95	7.39 (0.93 to 58.7)	77%	24% more (from 1.9% less to 28% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether proteinuria is a prognostic factor
Increased AST levels	1[26]	93	0.28 (0.04 to 1.71)	17%	30% less (from 50% less to 12.6% more)	**Very Low‡§** ⊕⊖⊖⊖	It is uncertain whether increased AST is a prognostic factor.
Leucocytosis	7[26 30 32 33 38 40 47]	1956	1.28 (1.01 to 1.62)	46%	5.8% more (from 0.2% more to 10.7% more)	**Low*** ** ⊕⊕⊖⊖	Leucocytosis may be a prognostic factor.

Continued

Table 3 Continued

Prognostic factor	Number of studies	Number of participants	OR (95% CI)	Prevalence of the factor studied in the population (%)	Risk difference with PF (%)	Overall certainty	Summary of the candidate prognostic factor
increased plasma LDH	1[26]	87	0.59 (0.08 to 4.02)	66%	15% less (from 90% less to 21% more)	**Very Low**‡ ⊕⊖⊖⊖	It is uncertain whether increased LDH is a prognostic factor.
Radiological findings							
Infiltrates on chest radiography	5[27 30 38 40 47]	1869	5.18 (2.15 to 12.52)	51%	25.5% more (from 15.5% more to 30% more)	**Moderate***** ⊕⊕⊕⊖	The presence of pulmonary infiltrates on chest radiography is probably a prognostic factor.

High (⊕⊕⊕⊕) We are very confident about this prognostic factor.
Moderate (⊕⊕⊕⊖) We are somewhat confident about this prognostic factor.
Low (⊕⊕⊖⊖) We are not very confident about this prognostic factor.
Very low (⊕⊖⊖⊖) We are uncertain about this prognostic factor.
*Risk of bias: not downgraded; results remained robust after excluding high-risk-of-bias studies (with unadjusted estimates).
†Based on low and some concerns risk of bias studies providing adjusted estimates; downgraded one level for imprecision (exposure did not meet optimal information size).
‡Imprecision (severe): downgraded two levels; 95% CI crosses the decision threshold and is compatible with benefit, no effect and harm.
§Risk of bias: downgraded one level (most contributing estimates from high-risk-of-bias studies that provided unadjusted estimates).
¶Imprecision: downgraded one level; 95% CI crosses the decision threshold and is compatible with no effect and harm.
**Inconsistency: downgraded one level for unexplained visual heterogeneity.
AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PF, prognostic factor.

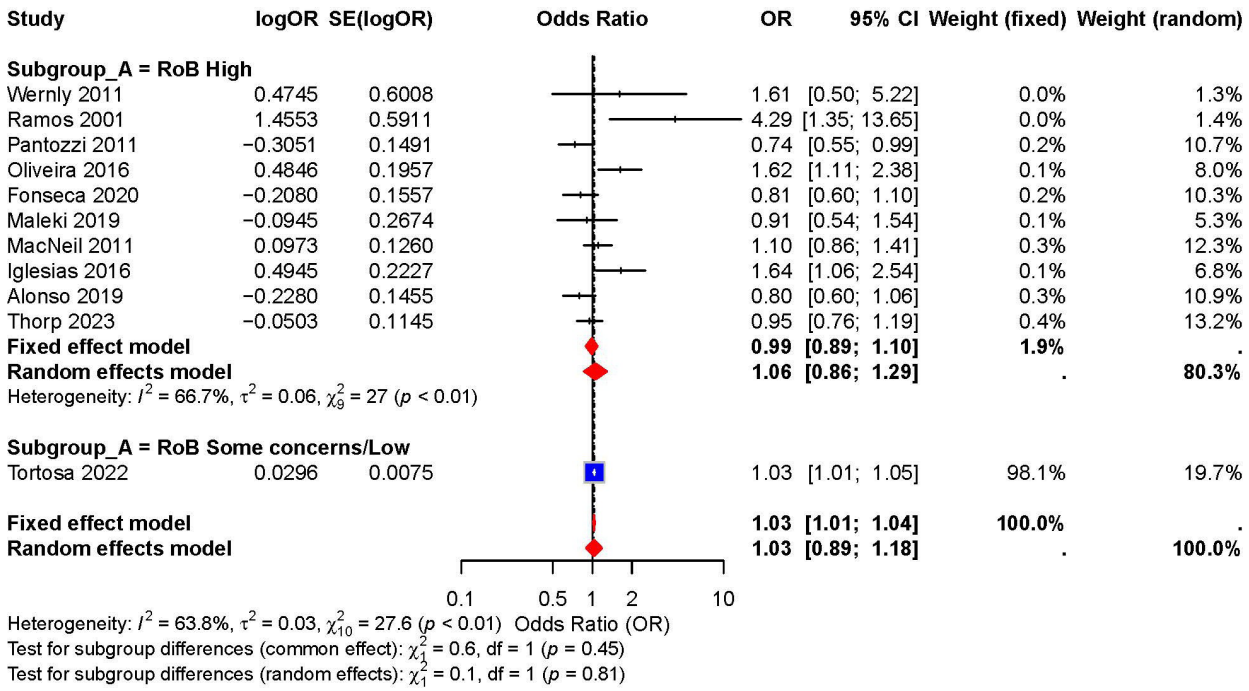

Figure 2 Forest plot: Age more than 18 years and mortality. Random-effects meta-analysis in HPS comparing patients older than 18 years with those 18 years or younger. Squares are proportional to study weight and diamonds indicate pooled effects; bold values represent pooled odds ratios and 95% confidence intervals derived from fixed-effect and random-effects meta-analysis models. Subgroups are by RoB category (high vs some concerns/low). Outcome: in-hospital mortality (or 28–30 days). df, degrees of freedom; HPS, hantavirus pulmonary syndrome; I², heterogeneity; RoB, risk of bias; τ², between-study variance; χ², Cochran's Q.

Elevated serum creatinine

This factor was evaluated in 6 studies[26 27 30 33 39 42] including 679 participants. Elevated plasma creatinine was defined using thresholds between >1.2 and >1.6 mg/dL. Elevated plasma creatinine is probably a prognostic factor for mortality (OR 2.52; 95% CI 1.47 to 4.34), with an ARD 18.5% higher (95% CI from 9% to 25.2% higher) and moderate certainty (⊕⊕⊕⊖). We downgraded one level of certainty for unexplained inconsistency (online supplemental figure S37).

Proteinuria

This factor was evaluated in 1 study[34] with 95 participants. It is uncertain whether the presence of proteinuria is a prognostic factor for mortality (OR 7.39; 95% CI 0.93 to 58.7), with an ARD 32.3% higher (from 1.6% lower to 40% higher) and very low certainty of the evidence (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB (online supplemental figure S6).

Thrombocytopenia

This factor was evaluated in 8 studies[23 26 30–33 39 47] including 1117 participants. A low platelet count was variably defined as ≤30 000 /mm³, <100 000/mm³, ≤150 000 /mm³ or as unspecified thrombocytopenia. A decreased platelet count may be a prognostic factor for mortality (OR 1.44; 95% CI 0.82 to 2.60), with an ARD 7.7% higher (95% CI from 5.3% lower to 16.2% higher) and low certainty (⊕⊕⊖⊖). We downgraded two levels of certainty for severe imprecision (online supplemental figure S38).

Leucocytosis

This factor was evaluated in 7[26 30 32 33 38 40 47] studies including 1956 participants. Leucocytosis (elevated white blood cell count) was variously defined, with cut-offs such as >12 000/mm³ and >11 000/mm³; several studies did not specify an exact threshold. Leucocytosis may be a prognostic factor for mortality (OR 1.28; 95% CI 1.01 to 1.62), with an ARD 5.8% higher (95% CI from 0.2% to 10.7% higher) and low certainty (⊕⊕⊖⊖). We downgraded one level of certainty for unexplained inconsistency and one level for RoB (online supplemental figure S10).

Elevated AST levels

This factor was evaluated in 1 study[26] in 81 participants. It is uncertain whether elevated aspartate aminotransferase (AST) is a prognostic factor for mortality (OR 2.4; 95% CI 0.91 to 6.35), with an ARD 19.9% higher (from 2.1% lower to 37.3% higher) and very low certainty (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB (online supplemental figure S7).

Elevated plasma LDH

Only one study[26] assessed elevated plasma lactate dehydrogenase (LDH) in 87 patients. Elevated LDH was defined

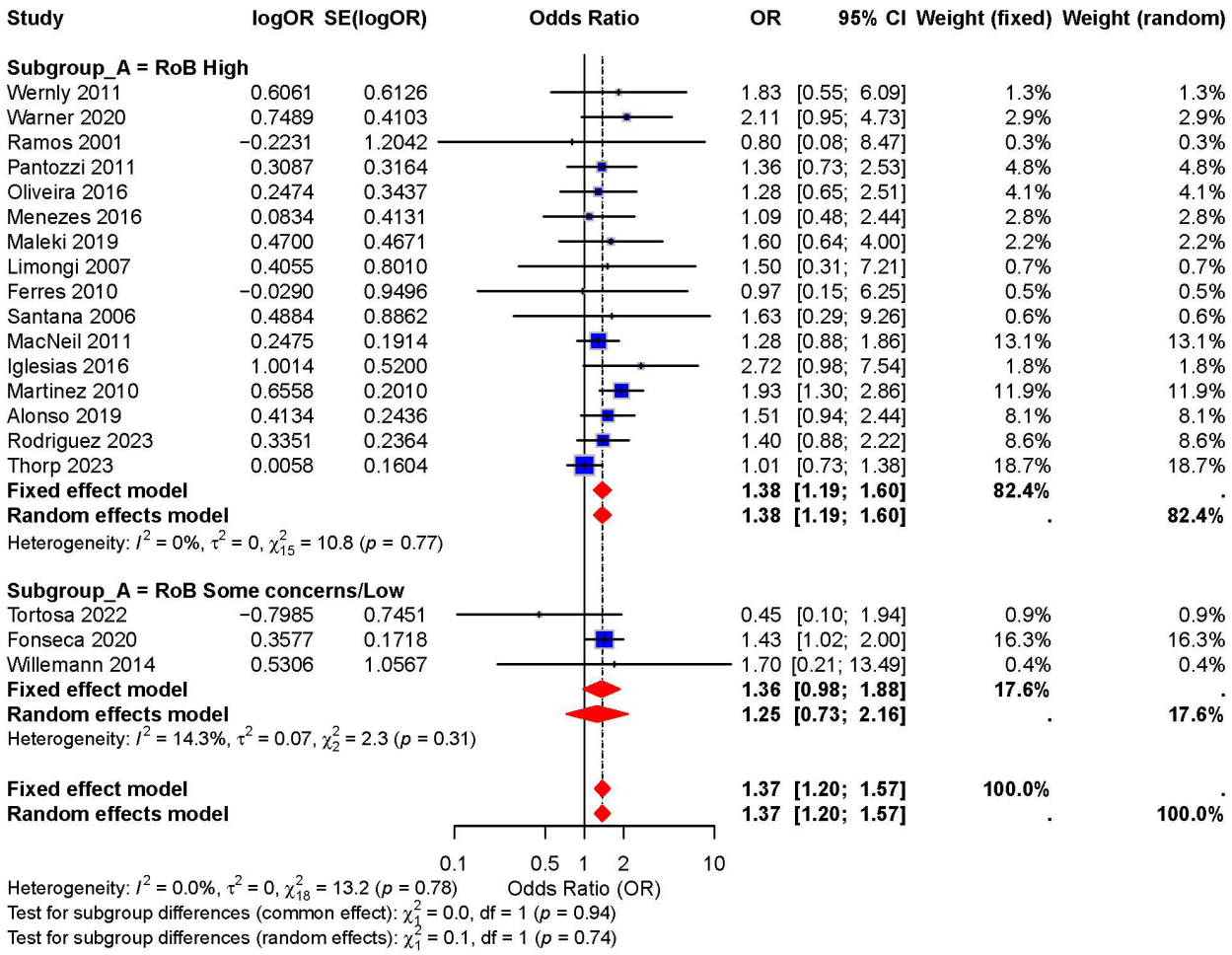

Figure 3 Forest plot: Female sex and mortality. Random-effects meta-analysis in HPS comparing females with males. Squares are proportional to study weight and diamonds indicate pooled effects; bold values represent pooled odds ratios and 95% confidence intervals derived from fixed-effect and random-effects meta-analysis models. Subgroups are by RoB category (high vs some concerns/low). Outcome: in-hospital mortality (or 28–30 days). df, degrees of freedom; HPS, hantavirus pulmonary syndrome; I², heterogeneity; RoB, risk of bias; τ², between-study variance; χ², Cochran's Q.

as >500 U/L on laboratory testing. It is very uncertain whether elevated plasma LDH is a prognostic factor for mortality (OR 0.59; 95% CI 0.08 to 4.02), with an ARD 15% lower (95% CI from 90% lower to 21% higher) and very low certainty (⊕⊖⊖⊖). We downgraded two levels of certainty for severe imprecision and one level for RoB.

Additional analysis

Results were robust in sensitivity analyses that excluded high-RoB studies, with the one exception for the rural (vs urban) comparison, where excluding estimates from high RoB studies (providing unadjusted estimates) shifted the pooled effect; therefore, we used the pooled estimates from studies classified as 'some concerns' in the RoB assessment (those with adjusted estimates) (online supplemental figures S22–43). We also conducted a sensitivity analysis to assess the impact of potential cohort overlaps; after excluding cohorts with suspected overlap, effect estimates remained robust. Subgroup analyses across New World hantavirus species found no consistent evidence of effect modification for any candidate prognostic factor; estimates were broadly similar across species (online supplemental figures S11–21).

DISCUSSION

This systematic review identified several prognostic factors associated with increased mortality in individuals with New World hantavirus infection. These factors, supported by moderate to high certainty evidence, include female sex, elevated creatinine levels, increased haematocrit, rural (vs urban) residence, clinical signs of bleeding and the presence of infiltrates on chest radiographs. Several of these factors (elevated haematocrit and creatinine, signs of bleeding and presence of infiltrates on chest radiographs) are consistent with capillary leakage and evolving multiorgan dysfunction, which plausibly explains their association with higher mortality.[49] An imbalance in immune response, characterised by heightened inflammatory cytokines without effective regulation, contributes to these severe clinical manifestations and increased mortality risk in these patients.[1 32 50] Rural

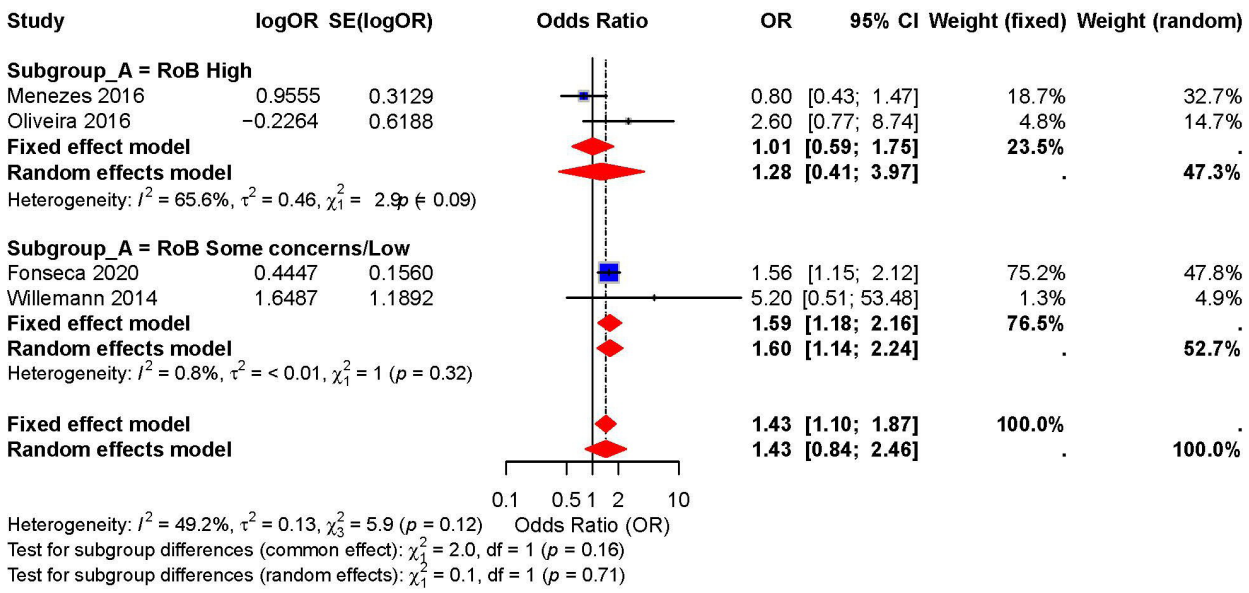

Figure 4 Forest plot: Rural residence and mortality. Random-effects meta-analysis in HPS comparing rural with urban residence. Squares are proportional to study weight and diamonds indicate pooled effects; bold values represent pooled odds ratios and 95% confidence intervals derived from fixed-effect and random-effects meta-analysis models. Subgroups are by RoB category (high vs some concerns/low). Outcome: in-hospital mortality (or 28–30 days). df, degrees of freedom; HPS, hantavirus pulmonary syndrome; I², heterogeneity; RoB, risk of bias; τ², between-study variance; χ², Cochran's Q.

residence association with higher mortality risk was likely mediated by barriers to timely and effective care (longer intervals to initial assessment, delays in referral or transfer from remote areas, and limited critical-care capacity) rather than by intrinsic viral characteristics.[51] The excess risk among women may reflect biological differences, residual confounding or differences in care pathways; clarifying these mechanisms will require analyses with harmonised adjustment for comorbidity burden and baseline severity.[42 45]

Consistent with other studies, age >18 years was not associated with increased mortality.[41 42] Notably, most included cohorts had mean ages around 35 years, with few participants in older age bands; this distribution and the low, non-informative cut-point likely limited our ability to detect risk concentrated at advanced ages. Given

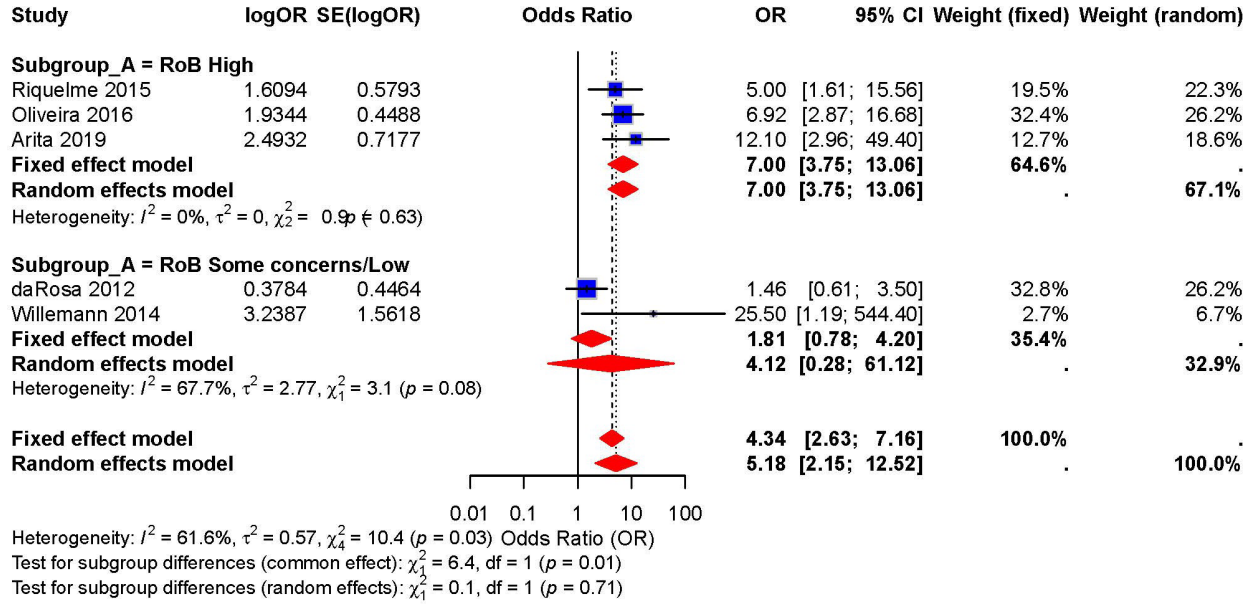

Figure 5 Forest plot: Infiltrates observed on chest radiograph and mortality. Random-effects meta-analysis in HPS comparing presence versus absence of chest-radiograph infiltrates. Squares are proportional to study weight and diamonds indicate pooled effects; bold values represent pooled odds ratios and 95% confidence intervals derived from fixed-effect and random-effects meta-analysis models. Subgroups are by RoB category (high vs some concerns/low). Outcome: in-hospital mortality (or 28–30 days). df, degrees of freedom; HPS, hantavirus pulmonary syndrome; I², heterogeneity; RoB, risk of bias; τ², between-study variance; χ², Cochran's Q.

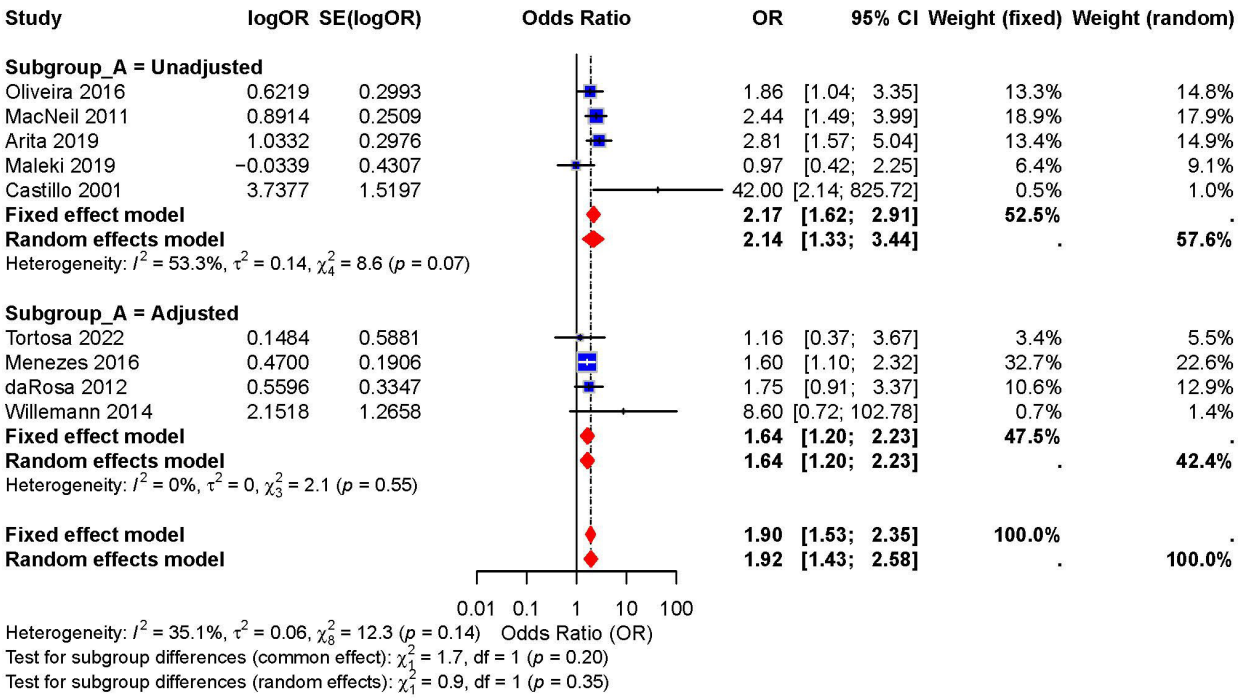

Figure 6 Forest plot: Elevated haematocrit and mortality. Random-effects meta-analysis in HPS comparing elevated versus not elevated haematocrit. Squares are proportional to study weight and diamonds indicate pooled effects; bold values represent pooled odds ratios and 95% confidence intervals derived from fixed-effect and random-effects meta-analysis models. Subgroups are by RoB category (high vs some concerns/low). Outcome: in-hospital mortality (or 28–30 days). df, degrees of freedom; HPS, hantavirus pulmonary syndrome; I², heterogeneity; RoB, risk of bias; τ², between-study variance; χ², Cochran's Q.

biological plausibility and patterns in other infections,[52] modelling age as a continuous predictor or using higher thresholds (eg, ≥60 years) may prove discriminative; however, adjusted data stratified by such cut-points were too sparse to permit a definitive analysis and should be prioritised in future work.

In addition to these high-certainty factors, our review identified several potential prognostic factors with lower certainty, such as thrombocytopenia, leucocytosis, vomiting, prolonged symptoms (more than 5 days), obesity and elevated liver transaminases (AST and alanine aminotransferase (ALT)). Meta-analyses for these variables showed moderate-to-substantial heterogeneity; thus, pooled estimates should be interpreted cautiously. While clinically plausible markers of severity, the evidence is limited and larger, prospectively collected datasets with adjusted analyses are needed to establish prognostic relevance.

We did not identify any systematic reviews focused on patients with New World hantaviruses. However, we identified two reviews in Old World hantaviruses causing HFRS that serve as relevant comparators.[53 54] For example, Huttunen *et al* identified prognostic associations in HFRS that are largely concordant with our findings: bleeding manifestations—including gastrointestinal and intracranial haemorrhage—prolonged PT/APTT and thrombocytopenia among non-survivors. Important differences also emerge. Unlike HPS, where elevated serum creatinine is a prognostic factor, Lu *et al* found no significant differences in serum creatinine in HFRS; early renal involvement was better captured by proteinuria and reduced urine output. Moreover, the HFRS literature placed greater emphasis on comorbidities (hypertension, diabetes) and additionally identified older age (≥60 years) and smoking as risk factors—variables not consistently reported in the New World hantavirus studies included in our review. Finally, neither review reported absolute effect estimates (eg, baseline risks, RDs or predicted probabilities) to support clinical decision-making, nor did they apply the GRADE approach adapted for prognostic factors to rate the CoE for each candidate prognostic factor.

While several key prognostic factors were identified, this review has limitations. First, the included studies were retrospective and varied in quality, with several failing to control for potential confounders such as disease severity at presentation or pre-existing conditions, which may bias estimates and limit generalisability. Moreover, differences in diagnostic methods and patient populations across studies likely contributed to between-study heterogeneity. A further limitation is the potential overlap of patient cohorts across some reports. We sought to mitigate these issues by rating certainty using a GRADE framework and by conducting prespecified sensitivity analyses (eg, restricting to adjusted estimates, excluding high-RoB studies) and subgroup analyses (eg, by viral species); however, some residual impact on the observed results is likely.

Despite these limitations, this is, to our knowledge, the first review focused on New World hantavirus infections that applies a prospectively registered protocol, a comprehensive multidatabase search, QUIPS for RoB assessment and a GRADE-based framework adapted to prognostic research to rate certainty and translate relative effects into ARDs.

In conclusion, our systematic review identified key prognostic factors for mortality in New World hantavirus infection, which can assist clinicians in making better management decisions. These findings also provide a foundation for developing a clinical prognostic model, with the potential to improve patient care and outcomes.

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REFERENCES

1 Borges AA, Campos GM, Moreli ML, *et al*. Hantavirus cardiopulmonary syndrome: immune response and pathogenesis. *Microbes Infect* 2006;8:2324–30.
2 Giebel LB, Raab K, Zöller L, *et al*. Identification and characterization of a Hantavirus strain of unknown origin by nucleotide sequence analysis of the cDNA derived from the viral S RNA segment. *Virus Genes* 1991;5:111–20.
3 Pini N. Hantavirus pulmonary syndrome in Latin America. *Curr Opin Infect Dis* 2004;17:427–31.
4 Jenison S, Hjelle B, Simpson S, *et al*. Hantavirus pulmonary syndrome: clinical, diagnostic, and virologic aspects. *Semin Respir Infect* 1995;10:259–69.
5 Hjelle B, Torres-Pérez F. Hantaviruses in the americas and their role as emerging pathogens. *Viruses* 2010;2:2559–86.
6 Enria DA. Emergencia de los hantavirus en las Americas y en la Argentina. *Med BAires* 1998;58:15–8.
7 Figueiredo LTM, Souza WM de, Ferrés M, *et al*. Hantaviruses and cardiopulmonary syndrome in South America. *Virus Res* 2014;187:43–54.
8 Crowley MR, Katz RW, Kessler R, *et al*. Successful treatment of adults with severe Hantavirus pulmonary syndrome with extracorporeal membrane oxygenation. *Crit Care Med* 1998;26:409–14.
9 Kaya S. Prognostic factors in hantavirus infections. *Mikrobiyol Bul* 2014;48:179–87.
10 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
11 Rayner DG, Kim B, Foroutan F. A brief step-by-step guide on conducting a systematic review and meta-analysis of prognostic model studies. *J Clin Epidemiol* 2024;170:111360.
12 Moons KG, Hooft L, Williams K, *et al*. Implementing systematic reviews of prognosis studies in Cochrane. Cochrane Library. Available: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.ED000129/full [Accessed 22 Oct 2025].
13 Cochrane handbook for systematic reviews of interventions. Cochrane. Available: https://www.cochrane.org/authors/handbooks-and-manuals/handbook?utm_source=chatgpt.com [Accessed 22 Oct 2025].
14 Moons KGM, de Groot JAH, Bouwmeester W, *et al*. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;11:e1001744.
15 Tortosa F. Prognostic factors for severity and mortality in patients infected hantavirus: a systematic review protocol. CRD42021225823. PROSPERO Int Prospect Regist Syst Rev; 2020. Available: https://www.crd.york.ac.uk/prospero/export_details_pdf.php [Accessed 23 Jul 2024].
16 Iorio A, Spencer FA, Falavigna M, *et al*. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.
17 Hayden JA, van der Windt DA, Cartwright JL, *et al*. Assessing Bias in Studies of Prognostic Factors. *Ann Intern Med* 2013;158:280–6.
18 Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 2010;36:1–48.
19 Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014;348:f7450.
20 Wang Z. Converting Odds Ratio to Relative Risk in Cohort Studies with Partial Data Information. *J Stat Soft* 2013;55:1–11.
21 Foroutan F, Guyatt G, Zuk V, *et al*. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020;121:62–70.
22 Foroutan F, Iorio A, Thabane L, *et al*. Calculation of absolute risk for important outcomes in patients with and without a prognostic factor of interest. *J Clin Epidemiol* 2020;117:46–51.
23 Wernly JA, Dietl CA, Tabe CE, *et al*. Extracorporeal membrane oxygenation support improves survival of patients with Hantavirus cardiopulmonary syndrome refractory to medical treatment☆. *Eur J Cardiothorac Surg* 2011;40:1334–40.
24 Warner BM, Dowhanik S, Audet J, *et al*. Hantavirus Cardiopulmonary Syndrome in Canada. *Emerg Infect Dis* 2020;26:3020–4.
25 Vial CC, Valdivieso RF, Cuiza VA, *et al*. Sociodemographic risk factors of hantavirus cardiopulmonary syndrome. *Rev Chil Infectologia Organo Of Soc Chil Infectologia* 2019;36:428–32.
26 Tortosa F, Carrasco G, Gallardo D, *et al*. Prognostic factors for cardio-pulmonary syndrome and death by hantavirus Andes Sur: cohort study in San Carlos de Bariloche and health influence area. *Medicina (B Aires)* 2022;82:351–60.

27 Riquelme R, Rioseco ML, Bastidas L, *et al*. Hantavirus pulmonary syndrome, Southern Chile, 1995-2012. *Emerg Infect Dis* 2015;21:562–8.
28 Ramos MM, Overturf GD, Crowley MR, *et al*. Infection with Sin Nombre hantavirus: clinical presentation and outcome in children and adolescents. *Pediatrics* 2001;108:E27.
29 Pantozzi F, Bolzán A, Masana M. Perfil clínico epidemiológico de infección por hantavirus en la Provincia de Buenos Aires, Argentina, periodo 1996 – 2009. *Revista Chilena de Salud Pública* 1996;15:155–64.
30 Oliveira RC, Sant'ana MM, Guterres A, *et al*. Hantavirus pulmonary syndrome in a highly endemic area of Brazil. *Epidemiol Infect* 2016;144:1096–106.
31 Menezes Filho HR, Moreli ML, Sousa AL, *et al*. Cross-sectional study on case fatality rate due to hantavirus infection in Goiás State, Brazil, 2007-2013. *Epidemiol E Serv Saude Rev Sist Unico Saude Bras* 2016;25:519–30.
32 Maleki KT, García M, Iglesias A, *et al*. Serum Markers Associated with Severity and Outcome of Hantavirus Pulmonary Syndrome. *J Infect Dis* 2019;219:1832–40.
33 MacNeil A, Ksiazek TG, Rollin PE. Hantavirus Pulmonary Syndrome, United States, 1993–2009. *Emerg Infect Dis* 2011;17:1195–201.
34 López R, Espinoza M, Graf J, *et al*. Proteinuria in Hantavirus Cardiopulmonary Syndrome: A Frequent Finding Linked To Mortality. *Int J Infect Dis* 2021;110:466–8.
35 Limongi JE, da Costa FC, de Paula MBC, *et al*. Hantavirus cardiopulmonary syndrome in the Triângulo Mineiro and Alto Paranaíba regions, State of Minas Gerais, 1998-2005: clinical-epidemiological aspects of 23 cases. *Rev Soc Bras Med Trop* 2007;40:295–9.
36 Iglesias AA, Bellomo CM, Martínez VP. Hantavirus pulmonary syndrome in Buenos Aires, 2009-2014. *Medicina (B Aires)* 2016;76:1–9.
37 Fonseca LX, Duarte EC, Oliveira SV de. Fatores prognósticos associados ao óbito por hantavirose no Brasil, 2007 a 2015. *J Health Biol Sci* 2020;8:1–8.
38 da Rosa Elkhoury M, da Silva Mendes W, Waldman EA, *et al*. Hantavirus pulmonary syndrome: prognostic factors for death in reported cases in Brazil. *Trans R Soc Trop Med Hyg* 2012;106:298–302.
39 Castillo C, Naranjo J, Sepúlveda A, *et al*. Hantavirus pulmonary syndrome due to Andes virus in Temuco, Chile: clinical experience with 16 adults. *Chest* 2001;120:548–54.
40 Arita DA, Shimakura SE. Survival of persons with hantavirus infection diagnosed in Paraná State, Brazil. *Cad Saude Publica* 2019;35:e00105518.
41 Ferrés G M, Sandoval C C, Delgado B I, *et al*. Hantavirosis: clinical and epidemiological characteristics of pediatric patients in Chile. *Rev Chilena Infectol* 2010;27:52–9.
42 Santana R de C, Campos GM, Figueiredo LTM, *et al*. Clinical and laboratory findings related to a favorable evolution of hantavirus pulmonary syndrome. *Rev Soc Bras Med Trop* 2006;39:237–40.
43 Martinez VP, Bellomo CM, Cacace ML, *et al*. Hantavirus pulmonary syndrome in Argentina, 1995-2008. *Emerg Infect Dis* 2010;16:1853–60.
44 Thorp L, Fullerton L, Whitesell A, *et al*. Hantavirus Pulmonary Syndrome: 1993-2018. *Pediatrics* 2023;151:e2022059352.
45 Alonso DO, Iglesias A, Coelho R, *et al*. Epidemiological description, case-fatality rate, and trends of Hantavirus Pulmonary Syndrome: 9 years of surveillance in Argentina. *J Med Virol* 2019;91:1173–81.
46 Rodríguez A. A, Bolzán A, Pamparana C. Infección por hantavirus en la Provincia de Buenos Aires-Argentina. Comportamiento de la serie temporal 1997-2021. *Rev chil infectol* 2023;40:213–9.
47 Willemann MCA, de Oliveira S. Risk factors associated with hantavirosis fatality: a regional analysis from a case-control study in Brazil. *Rev Soc Bras Med Trop* 2014;47:47–51.
48 Ferres M, Vial P, Marco C, *et al*. Prospective evaluation of household contacts of persons with hantavirus cardiopulmonary syndrome in Chile. *J Infect Dis* 2007;195:1563–71.
49 Simons P, Guo Y, Bondu V, *et al*. Longitudinal Assessment of Cytokine Expression and Plasminogen Activation in Hantavirus Cardiopulmonary Syndrome Reveals Immune Regulatory Dysfunction in End-Stage Disease. *Viruses* 2021;13:1597.
50 Morzunov SP, Khaiboullina SF, St Jeor S, *et al*. Multiplex Analysis of Serum Cytokines in Humans with Hantavirus Pulmonary Syndrome. *Front Immunol* 2015;6:432.
51 Lakhani HV, Pillai SS, Zehra M, *et al*. Systematic Review of Clinical Insights into Novel Coronavirus (CoVID-19) Pandemic: Persisting Challenges in U.S. Rural Population. *Int J Environ Res Public Health* 2020;17:4279.
52 Abel L, Casanova JL. Human determinants of age-dependent patterns of death from infection. *Immunity* 2024;57:1457–65.
53 Huttunen NP, Mäkelä S, Pokka T, *et al*. Systematic literature review of symptoms, signs and severity of serologically confirmed nephropathia epidemica in paediatric and adult patients. *Scand J Infect Dis* 2011;43:405–10.
54 Lu W, Kuang L, Hu Y, *et al*. Epidemiological and clinical characteristics of death from hemorrhagic fever with renal syndrome: a meta-analysis. *Front Microbiol* 2024;15:1329683.