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Proteinuria in Hantavirus Cardiopulmonary Syndrome: A Frequent Finding Linked To Mortality

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ABSTRACT

Objectives: To determine the relative frequency and prognosis value of proteinuria in hantavirus cardiopulmonary syndrome (HCPS) due to Andes virus.
Methods: This observational analytical study prospectively obtained data from patients admitted to 12 health centers in nine Chilean cities between 2001 and 2018. Only patients with confirmed Andes virus HCPS and laboratory characterization that included qualitative proteinuria determination at admission were considered.
Results: The database involved 175 patients, 95 of them had a measurement of urine protein at the time of hospital admission. They were mainly male (71%) and the median age was 35 [22-47] years. Median duration of the febrile prodromal time was 5 [4-7] days. Hospital length of stay and hospital mortality rate were 10 [7-14] days and 21.1%, respectively. Seventy-three patients (77%) were identified with proteinuria at admission, which was associated with increased mortality rate (26% versus 5%, p=0.036) and the relative risk was 1.3 [1.1-1.6], p=0.002.
Conclusions: Proteinuria is a frequent finding in patients with HCPS, which is associated with a higher mortality rate.

Hantavirus cardiopulmonary syndrome (HCPS) is a zoonosis caused by different strains of "New World" orthohantaviruses. Andes orthohantavirus (ANDV) is the primary etiological agent of HCPS in Chile and Argentina, where HCPS reaches mortality rates up to 40%. The main reservoir of ANDV is the long-tailed pygmy rice rat (*Oligoryzomys longicaudatus*), which transmits ANDV to humans, primarily by aerosolization of rodent excreta. Only ANDV has been associated to human-to-human transmission (Maningold et al., 2014).

After an incubation period that varies from 7 to 39 days, HCPS begins with a febrile prodrome lasting several days, followed by rapid onset of a cardiopulmonary phase characterized by respiratory failure and circulatory shock with myocardial dysfunction. A similar clinical picture has been described for orthohantavirus disease in North America (Maningold et al., 2014; López et al., 2019).

In Asia and Europe, "Old World" orthohantaviruses cause hemorrhagic fever with renal syndrome (HFRS), which has lower lethality ranging from <1% to 5% (Maningold et al., 2014). Proteinuria is reportedly to be virtually a pathognomonic finding in HFRS, and is associated with acute kidney injury severity and prognosis (Mantula et al., 2017; Clement et al 2019). Kidney injury in HCPS is less well defined and is considered to be a complication of circulatory dysfunction. Although some series describe the presence of proteinuria (Duchin et al., 1994), a link with severity has not

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Table 1
HCPS description and comparison according to proteinuria status.

Variables	All N = 95	Positive proteinuria N = 73	Negative proteinuria N = 22	Significance
Age, years, median [IQR]	35 [22–47]	35 [23–48]	33 [18–46]	0.675
Male, N (%)	67 (71)	52 (71)	15 (68)	0.794
Prodromal time, days, median [IQR]	5 [4–7]	5 [4–7]	6 [4–8]	0.883
SP, mmHg, median [IQR]	110 [100–121]	111 [100–122]	112 [99–122]	0.646
DP, mmHg, median [IQR]	67 [60–77]	70 [62–80]	66 [60–69]	0.191
Lactate, mmol/L, median [IQR]	2.1 [1.7–3.1]	2.4 [1.8–3.3]	2.0 [1.0–2.4]	0.113
Hematocrit, %, median [IQR]	45 [40–49]	45 [41–50]	43 [39–45]	0.055
Leukocytes, x1000/mL, median [IQR]	11.1 [7.9–17.2]	11.5 [8.1–17.9]	11.9 [7.6–12.4]	0.201
Platelets, x1000/mL, median [IQR]	53 [35–84]	46 [33–72]	72 [39–93]	0.057
LDH, U/L, median [IQR]	828 [560–1173]	853 [575–1206]	729 [422–1017]	0.101
Blood pH, median [IQR]	7.42 [7.35–7.45]	7.42 [7.35–7.46]	7.40 [7.34–7.45]	0.911
Serum creatinine, mg/dL, median [IQR]	1.0 [0.8–1.3]	1.1 [0.9–1.4]	0.9 [0.7–1.1]	0.026
ALT, U/L, median [IQR]	66 [43–112]	64 [41–110]	102 [58–120]	0.196
AST, U/L, median [IQR]	108 [66–112]	110 [66–178]	147 [56–184]	0.679
Amylase, U/L, median [IQR]	45 [34–74]	44 [34–69]	60 [36–78]	0.268
Hospital LOS, days, median [IQR]	10 [7–14]	10 [6–15]	11 [7–13]	0.655
Hospital mortality, N (%)	20 (21)	19 (26)	1 (5)	0.036

Abbreviations: SP, systolic arterial pressure; DP, diastolic arterial pressure; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LOS, length of stay
Prodromal time was defined as the number of days with fever before hospital admission

been explored. This study hypothesize that proteinuria at hospital admission may have a prognostic value in patients with HCPS.

This was an observational analytical study. The cohort comprised patients from a prospectively obtained database by the Hantavirus Program from the "Instituto de Ciencias e Innovación en Medicina" Facultad de Medicina, Clínica Alemana - Universidad del Desarrollo. All primary data considered for this study were collected in 12 health centers from nine Chilean cities between 2001 and 2018. The diagnosis of HCPS was confirmed in all cases by quantitative ELISA detecting ANDV-specific immunoglobulin M and/or by reverse-transcription PCR detecting ANDV RNA in blood samples. The institutional ethics board approved this non-interventional study with anonymized data and waived the informed consent requirement.

Only patients with HCPS and laboratory characterization that included qualitative proteinuria determination at admission were considered. The standard method to measure qualitative proteinuria detection was urine dipstick (LabStrip U11 Plus, 77 ElektronikaKft, Hungary), with lower detection limits of 30 mg/dl. Patients with HCPS were categorized as proteinuria positive or negative. Primary outcome was in-hospital mortality. Categorical variables are shown as number of patients with percentage in parentheses and compared by Fisher's exact test. Continuous variables are expressed as median [IQR] and compared by Mann-Whitney U test. Then, a multivariate regression analysis was performed. Significance was set at $p<0.05$.

From the 175 patients enrolled with HCPS, quantitative proteinuria was available in 95 at admission. They were mainly male (71%) and the median age in years was 35 [22-47]. Their median duration of the febrile prodrome was 5 [4-7] days. Hospital length of stay and hospital mortality rate were 10 [7-14] days and 21.1% (Table 1), respectively.

Seventy-three (77%) patients were identified with proteinuria at hospital admission. Compared with patients without proteinuria, no difference was found in clinical or laboratory variables, except in serum creatinine (Table 1). However, hospital mortality was higher in patients with proteinuria (26% versus 5%, p=0.036). The relative risk of death in HCPS patients with positive proteinuria was 1.3 [1.1-1.6] (p=0.002). In a multivariate regression analysis, proteinuria was associated with hospital mortality independently of gender, age, and severity (Table S1).

Our main findings are a high frequency of proteinuria in HCPS, which is associated with a higher mortality rate. In "Old World" orthohantavirus disease, renal involvement is a main target of infection, with interstitial nephritis being its main histological finding (Mustonen et al., 1994) and proteinuria has been associated with severity of kidney injury (Mantula et al., 2017). In HFRS caused by Puumala orthohantavirus, proteinuria at the moment of diagnosis, along with thrombocytopenia and elevated C-reactive protein, enabled prediction of risk of severe acute kidney injury in a large cohort of patients (Latus et al., 2015). Proteins from glomerular and tubular origin have been described (Meier et al., 2018), due to tubular cell dysfunction and impairment of both size- and charge-selectivity properties of the glomerular filter leading to increased glomerular permeability (Ala-Houhala et al., 2002).

"New World" orthohantaviruses cause a different syndrome, mainly affecting the lungs and heart. Renal involvement is less frequent, nevertheless kidney failure with proteinuria has recently been described in America (Chand et al., 2020). Increased lung permeability is a mayor finding, partly due to endothelial dysfunction (Maningold et al., 2014; López et al., 2019). A similar alteration in glomerular endothelial cells may explain a presumable role of positive proteinuria as a permeability marker. This supports the hypothesis of proteinuria as a prognostic factor in HCPS, although consistent glomerular involvement has not been systematically sought in biopsies from HCPS.

It is believed that this is the first study in patients with HCPS due to ANDV that provides data about frequency and prognostic value of proteinuria. Unlike HFRS, proteinuria appears to lack sensitivity in HCPS, but it is proposed that this simple test at admission may provide a tool to detect more severely ill patients with increased risk of death.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.07.026.

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