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Clinical Spectrum and Renal Outcome of Cryoglobulinemia in Hong Kong

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Key Points

- Hepatitis B is a common cause of cryoglobulinemia in southeast Asia as compared with hepatitis C in Western countries.
- The presence of cryoglobulinemia in hepatitis B is associated with a worse renal event-free survival.
- The renal prognosis of cryoglobulinemia appears to be affected by the underlying cause, with hepatitis B having a worse renal outcome.

Abstract

Background Cryoglobulinemia is a systemic disease and the clinical involvement is variable. The long-term renal outcome of cryoglobulinemia remains unclear, and most published series are from the Western world, with a high proportion of chronic hepatitis C. The objective is to determine the prevalence, causes, and renal outcome of cryoglobulinemia in Hong Kong.

Methods We reviewed 289 patients with cryoglobulinemia in the public hospital database of Hong Kong between 2000 and 2019. The renal event-free survival, dialysis-free survival, and overall survival were analyzed according to the underlying etiologies, and compared with 7483 patients who tested negative for cryoglobulinemia during the same period.

Results Among the patients with cryoglobulinemia, 68 (24%) had chronic hepatitis B, 69 (24%) had hepatitis C, and 14 (5%) paraproteinemia. They were followed for 62.7±58.0 months. The 5-year dialysis-free survival was 68%, 70%, 67%, and 83% for patients with cryoglobulinemia attributed to hepatitis B, hepatitis C, paraproteinemia, and unknown etiology, respectively (P=0.05), and their 5-year overall survival was 61%, 58%, 22%, and 72%, respectively (P=0.002). Among patients with hepatitis B, the group with cryoglobulin had a worse renal event-free survival than those without (36% versus 43%, P=0.005), although their dialysis-free survival and all-cause mortality were similar. For patients with hepatitis C or paraproteinemia, the presence of cryoglobulin did not affect the renal outcome.

Conclusions Hepatitis B is a common cause of cryoglobulinemia in southeast Asia, and the presence of cryoglobulinemia is associated with a worse renal event-free survival. The renal prognosis of cryoglobulinemia appears to be affected by the underlying cause, with hepatitis B having a worse renal outcome and patients with paraproteinemia having a worse overall survival than those with other causes of cryoglobulinemia.

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Introduction

Cryoglobulinemia is a systemic disease characterized by the presence of circulating Ig that precipitates at temperatures below 37°C (1,2). These precipitated Igs lead to the plugging of small arteries and capillaries, which then result in an inflammatory response, vasculitis, and ultimately infarction and necrosis of the surrounding tissues (1). Cryoglobulinemia is traditionally categorized by Brouet *et al.* (3) into three groups, according to the Ig composition. It is a useful classification as it tends to correlate with the underlying pathogenic mechanism and clinical manifestations, which can be variable, depending on the type of cryoglobulin and location of the precipitations. Although most patients tend to be asymptomatic, manifestations may include palpable purpura, arthralgias, fatigue, severe vasculitis with skin necrosis, GN, and involvement of the peripheral nerves, central nervous system, gastrointestinal tract, lungs, and myocardium (2).

Irrespective of Brouet's classification, however, renal involvement is a common manifestation in cryoglobulinemia. About 88%–100% of patients with

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cryoglobulinemia with renal impairment have proteinuria and hematuria (4,5), with membranoproliferative GN the most common histologic pattern (4). Renal failure occurs in 47%–63% of patients, which was reported to occur 2.6–4 years after the diagnosis (6,7).

However, the long-term renal prognosis of cryoglobulinemia is much determined by the underlying etiology. Most published series in this area are from the Western world, with a high proportion of cases caused by chronic hepatitis C infection (8). In contrast, chronic hepatitis B infection is common in southeast Asia, and is an important cause of cryoglobulinemia in this part of the world, but the prognostic implication of cryoglobulinemia in this clinical context is poorly studied. The aim of our present study is to determine the prevalence, underlying etiologies, and the renal outcome of cryoglobulinemia.

Materials and Methods

We reviewed the clinical data of all patients who had serum cryoglobulin levels checked in the hospital laboratories under the Hong Kong Hospital Authority between 2000 and 2019 by the Clinical Data Analysis and Reporting System. The Clinical Data Analysis and Reporting System is the electronic health care record database developed by the Hong Kong Hospital Authority and contains the medical records of all patients under the care of local public hospitals, which covers over 95% of the Hong Kong population. All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional research committee at which the studies were conducted and with the 1964 Declaration of Helsinki and its later amendments or comparable ethics standards. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (institutional review board approval number CRE-2019.399).

The method of evaluation of cryoglobulins has been described previously (9). In essence, clotted blood samples were collected and processed at 37°C. Two aliquots of serum were obtained, with one kept at 4°C and the other at 37°C. The serum samples were tested for cryoprecipitation by daily inspection at 4°C over 3 days and compared with the aliquot kept at 37°C. Cryoglobulin was confirmed by resolubilization on rewarming of the sample to 37°C, and further characterized by immunodiffusion or immunofixation. Cryoglobulin positivity was defined as the detection of cryoglobulin in at least one serum sample of a patient at any time. The testing method is standardized across all of the hospitals under hospital authority.

In addition to the serum cryoglobulin level, we also reviewed patients' baseline demographic and clinical data, which included their hepatitis B and C status, presence of paraproteinemia, complete blood count, liver and renal function, urine protein to creatinine ratio, serum complements, and Ig levels. Hepatitis B infection is defined as the presence of hepatitis B surface antigen (HBsAg), hepatitis B DNA, or the use of anti-hepatitis B therapy at any one time. Similarly, hepatitis C infection is defined by the presence of anti-hepatitis C antibody (Anti-HCV), hepatitis C RNA, or the use of direct-acting antivirals (DAAs).

Clinical Outcome

Follow-up information, including serial renal function and need for replacement therapy, of all patients were reviewed to December 31, 2019. The baseline starting point (time zero) was defined as the time of cryoglobulin testing. Primary outcomes are renal event-free survival and the rate of renal function decline. A renal event was defined as 30% decline in the eGFR as compared with baseline. The rate of eGFR decline was calculated by the least-squares regression method. Secondary outcome measures include dialysis-free survival and all-cause mortality. The events of dialysis-free survival analysis included the need of long-term dialysis or persistent eGFR <15 ml/min per 1.73 m^2.

Statistical Analyses

Statistical analysis was performed by SPSS software version 24.0 (SPSS Inc., Chicago, IL). Data are presented as mean±SD or median (interquartile range) as appropriate. Difference between groups were compared by t test, Kruskal-Wallis test, Mann–Whitney U test, or chi-squared test as appropriate. Survival rates were analyzed with Kaplan-Meier curves and compared by the Cox proportional hazards model. P values <0.05 were considered statistically significant. All probabilities were two tailed.

Results

There were 8063 patients who had their cryoglobulin status checked during the study period. We excluded 291 patients because of missing data, and the data of 7772 patients were analyzed. Of these, 289 patients were cryoglobulin positive. The baseline characteristics of the study population are described and compared in Table 1.

The underlying etiology of cryoglobulinemia is summarized in Figure 1. Among the 289 patients who were cryoglobulin positive, 68 (24%) were HBsAg positive, 69 (24%) were anti-HCV positive, and 14 (5%) had paraproteinemia. For the 7483 patients who had cryoglobulin checked but were negative, 950 (13%) were HBsAg positive, 613 (8%) were anti-HCV positive, and 63 (0.8%) had paraproteinemia. The incidences of HBsAg, anti-HCV, and paraproteinemia were all significantly higher in patients who were cryoglobulinemia positive than were negative ($P<0.001$ for all comparisons). For the entire study population, cryoglobulinemia was detected in 7%, 10%, and 18% of patients who were HBsAg, anti-HCV, and paraproteinemia positive, respectively.

Renal biopsy was performed in 32 patients who were cryoglobulin positive. The histologic diagnoses were membranoproliferative GN (22 patients), membranous nephropathy (four patients), IgA nephropathy (two patients), crescentic GN (one case), minimal change disease (one case), and acute interstitial nephritis (two patients).

Effect of Etiology on Clinical Outcome

The patients with cryoglobulinemia were followed for 62.7±58.0 months. During this period, 256 patients developed the composite renal end point (186 patients with 30% decline in the eGFR and 70 patients progressed to ESKD), 117 patients died. The median rate of eGFR decline was −1.69 ml/min per 1.73 m^2 per year (interquartile range, −5.28–0.41).

Table 1. Baseline clinical and biochemical characteristic of the study population[a]

Characteristic	Cryoglobulin Positive	Cryoglobulin Negative	*P* value
No. of patients	289	7483	
Age, yr	62.5±16.0	61.2±17.9	0.18
Male sex, no. of patients (%)	145 (50%)	3397 (45%)	0.11
Laboratory parameters			
Hemoglobin (g/dl)	10.8±2.2	11.5±2.4	<0.001
White blood cell ($\times 10^9$/L)	7.3±4.5	8.4±6.8	0.006
Platelet ($\times 10^9$/L)	221.7±114.3	244.8±126.7	0.003
Urea (mmol/L)	8.5±7.8	9.5±9.3	0.05
Creatinine (μmol/L)	134.1±177.5	156.2±195.5	0.05
eGFR (ml/min per 1.73 m^2)	81.6±54.4	82.5±107.4	0.90
Total protein (g/L)	71.4±15.4	69.9±11.7	0.12
Globulin (g/L)	38.9±13.6	36.2±9.6	0.002
Albumin (g/L)	32.6±8.3	33.6±8.6	0.05
Bilirubin (μmol/L)	15.3±44.1	15.3±33.9	0.97
Alkaline phosphatase (IU/L)	89.9±58.5	96.7±81.1	0.18
Alanine aminotransferase (IU/L)	40.1±93.6	41.7±126.7	0.83
Aspartate aminotransferase (IU/L)	88.7±301.1	67.9±283.0	0.46
Gamma-glutamyl transferase (IU/L)	135.4±235.2	136.6±195.1	0.96
Rheumatoid factor positive, no. of case (%)	60 (44.1%)	1012 (31%)	0.001
C3 (g/L)	0.89±0.44	1.01±0.36	<0.001
C4 (g/L)	0.19±0.16	0.25±0.12	<0.001
IgA (g/L)	3.11±2.13	3.76±2.89	0.13
IgG (g/L)	16.44±13.49	15.90±8.24	0.79
IgM (g/L)	6.62±14.01	2.09±5.81	0.03
Urine protein-creatinine ratio	3.30±4.13	2.86±4.03	0.39

[a]Data expressed as mean±SD.

The rates of renal event-free survival, progression to ESKD, and overall survival were compared among different etiologies of cryoglobulinemia (Figure 2). The 5-year renal event-free survival was 36%, 39%, 27%, and 47% for patients with cryoglobulinemia attributed to hepatitis B, hepatitis C, paraproteinemia, and unknown etiology, respectively (log rank test, $P=0.01$); the corresponding 5-year dialysis-free survival was 68%, 70%, 67%, and 83%, respectively (log rank test, $P=0.05$), and their 5-year overall survival was 61%, 58%, 22%, and 72%, respectively ($P=0.002$). The difference in the risk of progression to ESKD and overall survival among different etiologies was even more apparent at 10 years (Figure 2). There is also no significant difference in rate of eGFR decline among different etiologies (Table 2). The unadjusted hazard ratios by univariate Cox analysis for the development of various outcomes among different etiologies are summarized and compared in Table 3. Patients with cryoglobulinemia of unknown etiology had a significantly worse primary composite outcome, risk of progression to ESKD, and overall survival as compared with those with hepatitis B. There is no significant difference among the other etiology groups, except for patients with paraproteinemia, which had a worse overall mortality (hazard ratio, 3.36 (1.51–7.46), $P= 0.003$).

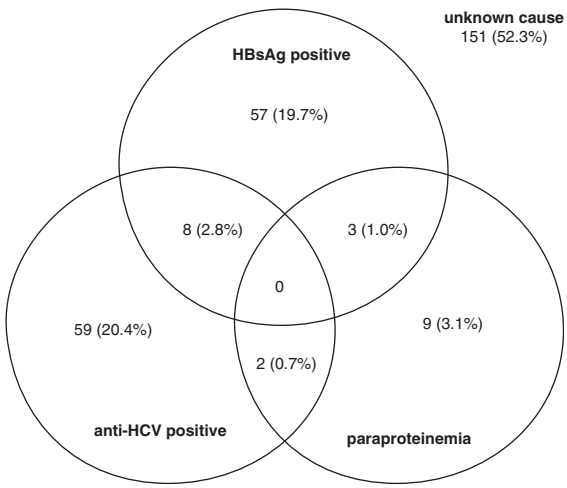

Figure 1. | Venn diagram of the underlying etiology for cryoglobulinemia. HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Effect of Antiviral Treatment on the Clinical Outcome with Viral Hepatitis

Among the 68 patients with cryoglobulinemia with hepatitis B, 58 (85%) were on antiviral treatment. For those with hepatitis C, 12 (17%) of the 69 patients received a myriad of DAAs. As for the cryoglobulinemia-negative group, 624 (66%) patients with hepatitis B and 66 (11%) patients with hepatitis C were on antivirals. The most commonly used antivirals for hepatitis B were entecavir and lamivudine, with only a few patients on tenofovir. Sofosbuvir/ledipasvir, glecaprevir/pibrentasvir, and ombitasvir/paritaprevir/ritonavir were the commonly used DAAs. None of the patients in our cohort received rituximab. The effect of these agents on the overall clinical outcome among

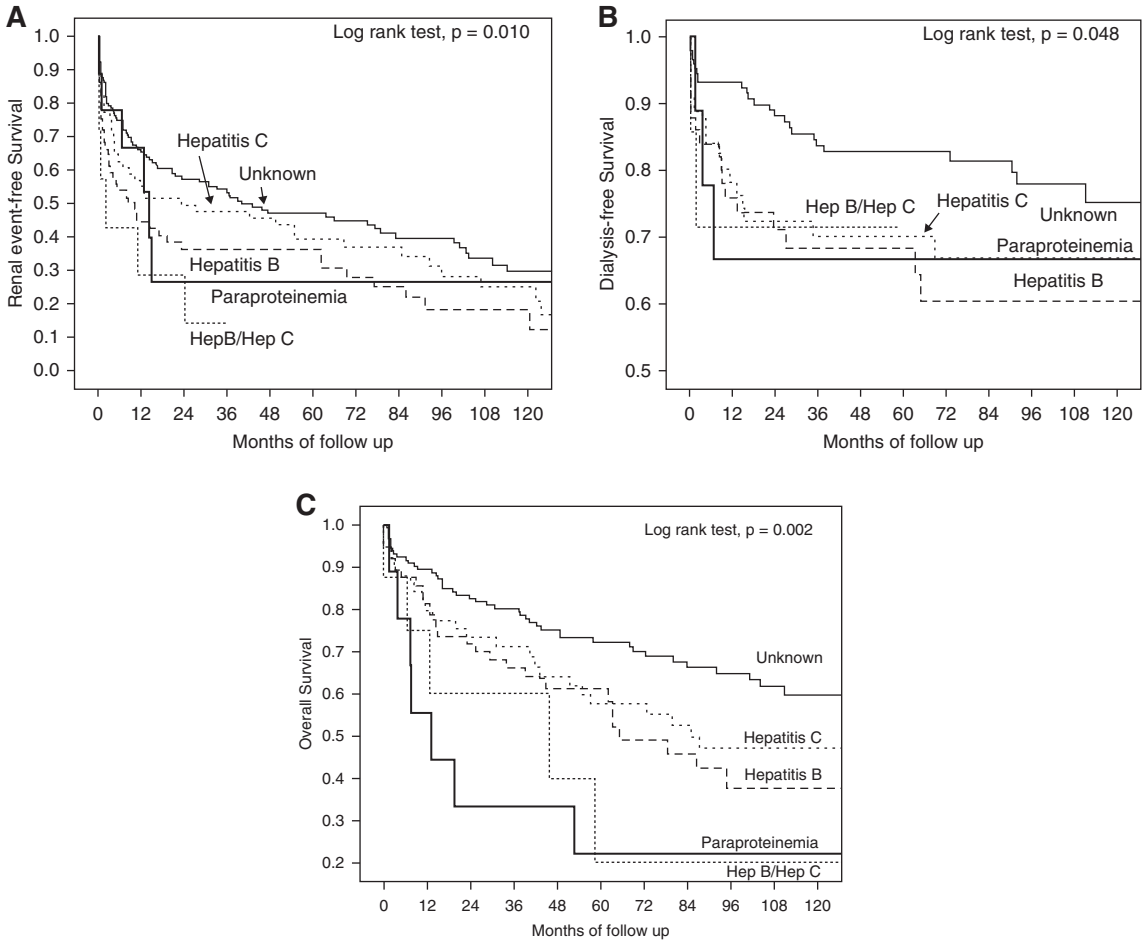

Figure 2. | **Kaplan-Meier plot of renal outcome.** (A) Renal event-free survival; (B) dialysis-free survival; and (C) overall survival. Data were compared by log-rank test.

hepatitis B and hepatitis C were also analyzed using the univariate Cox analysis. There was no statistical significance among primary composite end point, risk of progression to ESKD and overall survival irrespective of hepatitis B or C (Table 4).

Effect of Cryoglobulinemia on the Outcome of the Underlying Disease

The renal outcome was compared between patients with and without cryoglobulinemia, according to the underlying medical condition, as summarized in Figure 3. Among the patients who were HBsAg positive, the group with cryoglobulin had a worse 5-year renal event-free survival than those without (36% versus 43%, $P=0.005$), although the differences in dialysis-free survival and all-cause mortality did not reach statistical significance. For the patients who were anti-HCV positive, the presence of cryoglobulin did not appear to affect the clinical outcome (Figure 3). There is also no significant difference in the clinical outcome

Table 2. Rate of eGFR decline in patients with and without cryoglobulinemia according to their underlying diseases[a]

Etiology	eGFR Decline (Ml/min Per 1.73 m^2 Per Yr)		
	Cryoglobulin Positive[b]	Cryoglobulin Negative	*P* Value
Unknown	−2.18 (−6.36–0.15)	−1.33 (−4.65–0.75)	0.13
Hepatitis B	0.18 (−2.86–3.08)	−1.32 (−4.30–0.87)	0.26
Hepatitis C	−1.61 (−4.87–0.62)	−2.03 (−5.91–0.39)	0.49
Paraproteinemia	−0.24 (−8.37–7.52)	−1.21 (−5.76–0.36)	0.99

[a]Data expressed as median (interquartile range).
[b]Kruskal-Wallis test, $P=0.15$ for the comparison of cryoglobulin positive patients of different etiology groups.

Table 3. Univariate Cox analysis on the effect of various etiologies on the clinical outcome of patients with cryoglobulinemia

Etiology	Primary Composite End Point		Progression to ESKD		Overall Mortality	
	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value
Hepatitis B	0.59 (0.41 to 0.85)	0.004	0.46 (0.25 to 0.83)	0.01	0.54 (0.34 to 0.87)	0.01
Hepatitis C	0.79 (0.55 to 1.16)	0.23	0.57 (0.31 to 1.05)	0.07	0.67 (0.42 to 1.08)	0.10
Paraproteinemia	1.23 (0.53 to 12.81)	0.63	2.29 (0.69 to 7.61)	0.18	3.36 (1.51 to 7.46)	0.003

between the cryoglobulin positive and negative groups in patients with paraproteinemia.

Discussion

In this study, we found that chronic hepatitis B (in addition to chronic hepatitis C and paraproteinemia) is a common cause of cryoglobulinemia in southeast Asia. The renal prognosis of cryoglobulinemia appears to be affected by the underlying cause, with hepatitis B having a worse eventual renal outcome, and patients with paraproteinemia having a worse overall survival than those with other causes of cryoglobulinemia. The presence of cryoglobulinemia is also associated with worse renal event-free survival in patients with chronic hepatitis B-infection, as compared with those without cryoglobulinemia. In contrast, in patients with chronic hepatitis C or paraproteinemia, the presence of cryoglobulinemia does not appear to affect renal prognosis or survival.

One of the strengths of our study is the use of data from a large population-based, territory-wide database, with complete information on the underlying etiology and serial trend of renal function. As a result, it is a reliable estimate for the incidence of cryoglobulinemia in our population. Unlike previous reports from the Western population, our cohort has a high prevalence of hepatitis B-related cryoglobulinemia, which allows a better characterization of this disease entity.

The proportion of cryoglobulinemia secondary to chronic hepatitis C infection patients in our cohort is substantially lower than previous reports from the western countries (10,11), which generally showed that hepatitis C infection accounts for 50% to 70% patients of cryoglobulinemia. In contrast, hepatitis C infection was present in around 24% of our series. It should be noted that the prevalence anti-HCV in the general population is around 0.54%–2% in Western countries (12). In contrast, hepatitis C is less common in Hong Kong, with a prevalence of around 0.3% (13).

Our findings are similar to previous reports, which showed the survival rate is similar for both hepatitis C-related and noninfectious-related cryoglobulinemic vasculitis (10). However, the actual survival of our patients appears to be lower as compared with previous reports (14–17). The underlying cause of this discrepancy in survival is not entirely clear, but our cohort was slightly older than the other reports (15–17). Previous studies showed that age >65 years, renal involvement, and underlying hematologic malignancy are major predictors of poor survival in patients with cryoglobulinemia (15,16,18).

In this study, we found the presence of cryoglobulinemia does not affect the renal prognosis of patients with hepatitis C or paraproteinemia, but the presence of cryoglobulin was associated with a worse renal outcome among patients with hepatitis B infection (Figure 3). One possible reason is that hepatitis B may have a different mechanism of inducing renal damage as compared with hepatitis C. Although hepatitis B infection induces cryoglobulin formation in a similar way to hepatitis C (19), the differences in size and charge of the immune complexes may lead to their deposition in different compartments of the glomerulus and induce varying degrees of renal damage. Indeed, we found the renal outcome of cryoglobulinemia is worse with those in hepatitis B group, as already discussed (Figure 2). Furthermore, the renal outcome and overall survival appear to be even worse in the group of patients with cryoglobulinemia who are coinfected with both hepatitis B and hepatitis C (Figure 2). This is possibly due to the formation of immune complexes of many different mol wts with both hepatitis viruses. However, one should note that the number of coinfected patients may be too small, and further studies are needed. It should be noted that although hepatitis B infection is associated with an increased risk of CKD, it is

Table 4. Univariate Cox analysis on the effect of antivirals on the clinical outcome with either hepatitis B or hepatitis C

Etiology	Primary Composite End Point		Progression to ESKD		Overall Mortality	
	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value	Unadjusted Hazard Ratio (95% Confidence Interval)	*P* Value
Usage of antivirals in hepatitis B	0.49 (0.19 to 1.30)	0.15	0.722 (0.17 to 3.16)	0.67	0.60 (0.18 to 2.03)	0.42
Usage for DAA in hepatitis C	1.12 (0.53 to 2.38)	0.76	0.83 (0.27 to 2.56)	0.75	3.80 (0.90 to 16.1)	0.07

DAA, direct-acting antivirals.

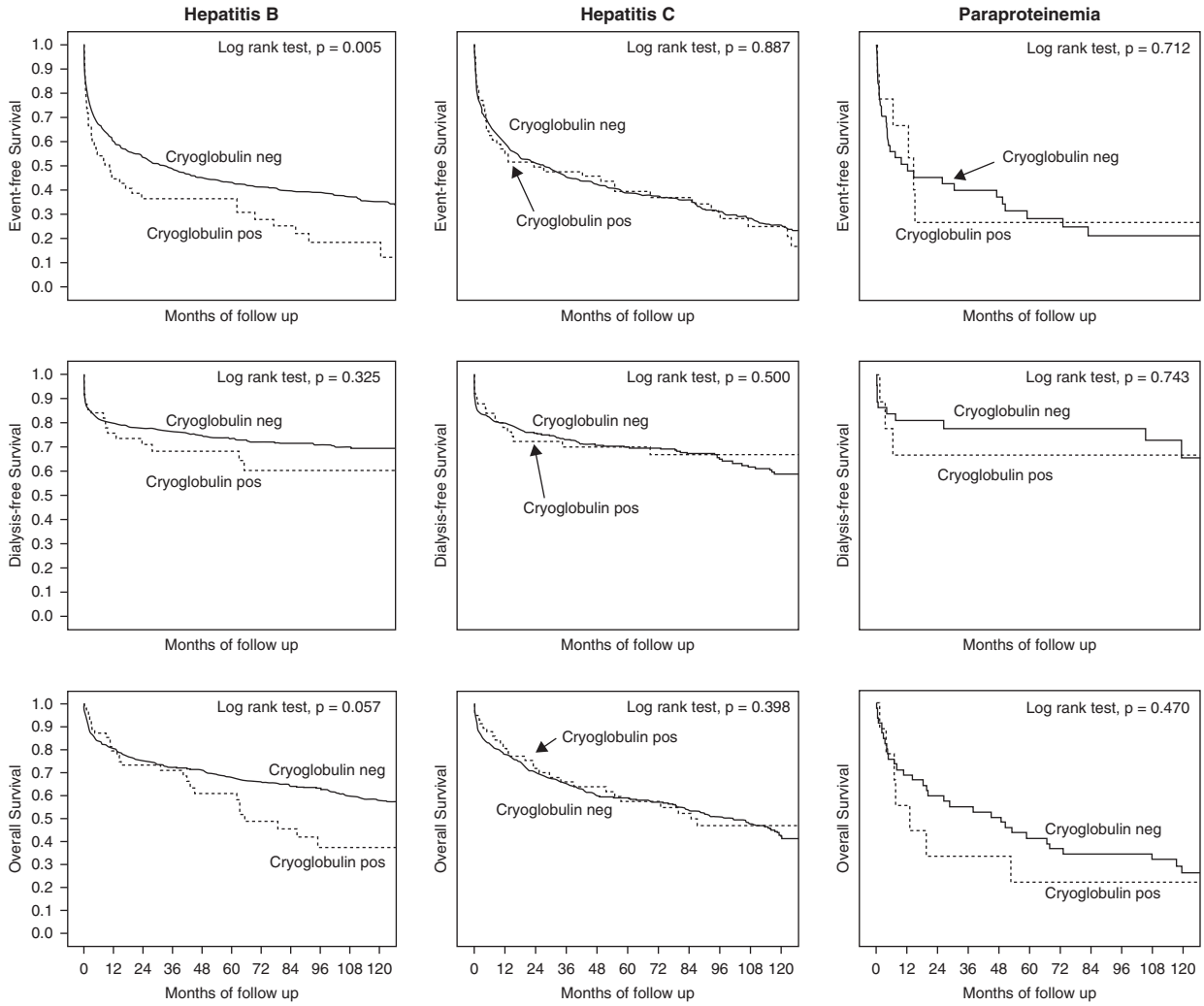

Figure 3. | **Comparison of renal outcome between patients with and without cryoglobulinemia, according to the underlying etiology.** Data were compared by log-rank test. neg, negative; pos, positive.

mostly the result of the associated GN or antiviral treatment (20), whereas the presence of hepatitis B infection does not appear to affect the progression of renal function loss in CKD of other etiologies (20–22). In contrast, coexistence of chronic hepatitis C infection causes more rapid loss of renal function for CKD due to other etiologies, irrespective to the presence of cryoglobulin (21,22), partly because hepatitis C infection causes glomerular hyperfiltration (23). Taken together, our result is consistent with the published literature and suggests that hepatitis C infection causes kidney damage by various mechanisms and the contribution of cryoglobulinemia is small. In contrast, hepatitis B infection does not cause kidney damage except *via* a few well-defined immunologic mechanisms, such as cryoglobulinemia.

In contrast, it was also possible we did not observe a prognostic effect in patients with cryoglobulinemia because of the limited sensitivity of our assay and an unknown proportion of the patients had a false-negative result. However, warm weather, especially in this part of the world, makes the possibility of inadvertent precipitation during sample transport seem less likely. Nonetheless, it has been argued that the cryoglobulin test may add little to the clinical decision, at least in patients with hepatitis C, because the treatment depends more on the clinical presentation and exact histologic pattern, rather than the presence of cryoglobulinemia (24).

There are several limitations in our study. Firstly, this is a retrospective study and there may be selection bias. However, we included all patients who had their cryoglobulin status checked within the study period. Second, we did not have the actual quantified level of cryoglobulins for analysis. Notably, Coliche *et al.* (25) recently reported that a higher level of cryoglobulin is associated with a higher risk of renal impairment, and for each increase of 100 mg/L of the total cryoglobulin level, the risk of renal involvement is increased by 10%. Similarly, Trejo *et al.* (8) reported that patients with a cryocrit >5% had a higher frequency of GN. More importantly, we do not have the data on the cause of death, major infections, cardiovascular events, or the information on treatment. Similarly, we do not have the data on the genotype of hepatitis C, and the genotype distribution of the virus is substantially different between countries (26).

However, there is no clear association between hepatitis C virus genotype and the risk of CKD progression (27). The information of other organ system involvement (*e.g.*, neuropathy, cutaneous vasculitis) and associated symptoms are also not available, but may be important for the overall assessment of the disease process.

In summary, our study showed that chronic hepatitis B is a common cause of cryoglobulinemia in southeast Asia, and, unlike chronic hepatitis C, the presence of cryoglobulinemia adversely affects the renal prognosis of patients with chronic hepatitis B.

Disclosures

C.-C. Szeto reports having consultancy agreements with Baxter Healthcare and Gilead Science; reports receiving research funding from Baxter Healthcare, Fibrogen Inc., Fresnius, and Gilead; reports receiving honoraria from Baxter Healthcare; reports being a scientific advisor or member of Baxter Healthcare and Gilead Science; and other interests/relationships with AstraZeneca and Pfizer. V.W.-S. Wong reports consultancy agreements with 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Inventiva, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, TARGET PharmaSolutions, and Terns; reports receiving research funding from Gilead Sciences; reports receiving honoraria from 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Inventiva, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, TARGET PharmaSolutions, and Terns; reports being a scientific advisor or member of the Clinical Gastroenterology and Hepatology and the editorial boards of the Journal of Hepatology, Hepatology, Alimentary Pharmacology and Therapeutics, Journal of Gastroenterology and Hepatology, JHEP Reports, and Hepatology Communications. All remaining authors have nothing to disclose.

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Author Contributions

G.L.-H. Wong conceptualized the study; K.-M. Chow, W.W.-S. Fung, G.L.-H. Wong, V.W.-S. Wong, and T.C.-F. Yip were responsible for data curation; W.W.-S. Fung was responsible for formal analysis, investigation, and methodology, and wrote the original draft; C.-C. Szeto provided supervision; and W.W.-S. Fung and C.-C. Szeto reviewed and edited the manuscript.

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