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Association of Cancer Antigen 125 with Long-Term Prognosis in Light-Chain Cardiorenal Amyloidosis

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Keywords
Light-chain cardiorenal amyloidosis · Cancer antigen 125 · Left ventricular longitudinal strain · Prognosis

Abstract
Introduction: Light-chain (AL) cardiorenal amyloidosis has been characterized as type 5 cardiorenal syndrome with fluid overload and poor prognosis. Cancer antigen 125 (CA125) has the potential for its use in evaluating fluid load and prognosis for heart failure. However, less details for CA125 in AL cardiorenal amyloidosis have been reported. ***Methods:*** Sixty patients diagnosed with AL cardiorenal amyloidosis were enrolled in this retrospective study. Patients were divided into two groups according to the cutoff point of CA125 level (35 U/mL). Logistic regression was used to screen variables associated with CA125. Cox regression analyses were utilized to verify the prognostic potential of CA125. ***Results:*** The mean age was 61 ± 8 years, and 68% of the participants were male. Compared to patients with normal CA125 levels (≤35 U/mL), patients with high levels of CA125 (>35 U/mL) had a higher proportion of New York Heart Association class >II, pericardial effusion, and edema, as well as a lower level of albumin and left ventricular longitudinal strain (LVLS). Logistic regression showed age, albumin, and LVLS to be independently associated with CA125. Seventeen (28%) patients died during the follow-up. Multivariate model including CA125, estimated glomerular filtration rate, E/e', and left ventricular ejection fraction showed acceptable prognostic potential (C-index = 0.829, 95% CI: 0.749–0.909). CA125 remained an independent prognostic factor (HR = 1.018, 95% CI: 1.005–1.031, $p = 0.008$, per 10 U/mL increase) after adjusting for the remaining three variates and provided a significant incremental effect to the risk determined from them (C-index 0.829 vs. 0.784, $p = 0.037$). ***Conclusion:*** Serum CA125 level was associated with long-term prognosis of AL cardiorenal amyloidosis.

Introduction

Systemic light-chain (AL) amyloidosis is characterized by misfolding and aggregation of proteins deposited in a variety of tissues, resulting in progressive multiple organ damage [1]. Cardiac and renal involvement are the most common in this disease. A previous study has reported that approximately 70% and 50% of systemic AL amyloidosis patients suffered from heart and kidney damage at diagnosis, respectively, and approximately 32% of patients were

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diagnosed with AL cardiorenal amyloidosis [2]. For patients with AL cardiorenal amyloidosis, organ cross-talk led to a further dysfunction of both organs, especially deteriorated congestive heart failure, which was characterized by volume overload [3]. Notably, the severity of cardiac dysfunction is the determinant of mortality [4].

In addition, discernible cardiac symptoms, such as progressive dyspnea on exertion or orthopnea, always appear in the late stage of a disease with poor prognosis [5]. Many patients turn to nephrologists rather than cardiologists because of complaints of edema and/or foamy urine with asymptomatic cardiac involvement. Due to the interference of renal function in the level of B-type natriuretic peptide (BNP) and N-terminal pro-B-type BNP (NT-pro BNP) [6], it is important to optimize the risk stratification in AL cardiorenal amyloidosis patients.

Cancer antigen 125 (CA125) is an acknowledged biomarker in ovarian cancer detection [7] that has also been documented in both acute and chronic heart failure. Serum CA125 level is not only superior to BNPs in assessing fluid load but is also a potential biomarker for therapeutic strategy and risk stratification in both acute and chronic heart failure [8–13].

However, no details for CA125 have been reported in AL cardiorenal amyloidosis patients characterized by involvement of multiple organs with organ cross-talk. The present study aimed to verify the prognostic value of CA125 for these patients and to analyze additional information over other variables.

Methods

Patients

Patients diagnosed with AL cardiorenal amyloidosis between July 2015 and November 2020 were enrolled in this retrospective study. The diagnostic criteria were as follows [14, 15]: (1) tissue biopsy results were positive for Congo Red staining: renal (n = 48), endocardium (n = 1), others (n = 11); and apple-green birefringence under polarized light, which was resistant to potassium permanganate pretreatment; (2) positive for monoclonal kappa or lambda protein upon serum/urine immunofixation electrophoresis or biopsy immunohistochemistry; (3) cardiac involvement was defined by positive endomyocardial biopsy or echocardiography-derived left ventricular (LV) mean wall thickness of ≥12 mm, with granular "sparkling" appearance of the myocardium. No other cardiac diseases that can cause hypertrophy; and (4) renal involvement defined as positive renal biopsy or non-Bence-Jones proteinuria >0.5 g/24 h.

This study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital, Medical School of Zhejiang University and was in accordance with the Declaration of Helsinki, approval number (2020IIT643). Informed consent was not necessary due to the retrospective nature of the study.

All patients were followed up at the clinic and/or by telephone. All-cause mortality was identified using electronic medical record as well as telephone contact. The time between the initial echocardiographic operation and death or last follow-up (December 2020) was registered as the follow-up period.

CA125 Assay

Serum CA125 levels were measured using an Architect i2000 platform (Abbott Diagnostics, Chicago, USA). The upper normal CA125 limit was set at 35 U/mL.

Echocardiography

Routine and speckle tracking two-dimensional echocardiography evaluations were performed (Vivid E9; GE Vingmed Ultrasound, Horten, Norway). LV interventricular septal and posterior wall thicknesses were measured in parasternal long-axis view. LV ejection fraction (LVEF) was measured using the biplane Simpson's method. LV longitudinal strain (LVLS) was calculated by averaging peak systolic longitudinal strain from three views (apical long-axis, two-chamber, and four-chamber) utilizing speckle tracing analysis. Peak mitral flow velocities during early diastole (E) measured in apical four-chamber view and early diastolic mitral annular velocity (e') at the lateral and septal sides measured by Tissue Doppler echocardiography were used to calculated E/e' ratio. Relative apical LVLS was defined as the average apical LVLS divided by the sum of the average mid-level and basal LVLS values. All strains were expressed as an absolute value.

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate the normality of variables. Normal continuous variables were represented as mean ± standard deviation and analyzed via Student's t test, while non-normal variables were represented as medians (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were represented as counts and percentages, which were analyzed with χ^2 or Fisher's tests.

Spearman's correlation analysis was used to illustrate the correlation between CA125 and other cardiac parameters. Logistic regression analysis was used to screen variables associated with CA125. Variates with a p value of <0.1 in the univariate logistic regression were incorporated into the multivariate analysis. Kaplan-Meier analysis was used to compare the cumulative mortality of AL cardiorenal amyloidosis patients with different CA125 levels, using log-rank and Gehan-Breslow-Wilcoxon test. Univariate and multivariate Cox regression analyses were used to verify the independent prognostic value of CA125. C-index was calculated to evaluate the prognostic potential of Cox models. Nested model analysis showed the incremental prognostic information of CA125 over other variates using likelihood-ratio test. All statistical analyses were performed using SPSS 23.0 and R (version 4.0.5) software. $p < 0.05$ was considered statistically significant.

Results

Clinical Characteristics of AL Cardiorenal Amyloidosis Patients

A total of 63 patients were diagnosed with AL cardiorenal amyloidosis between July 2015 and November 2020.

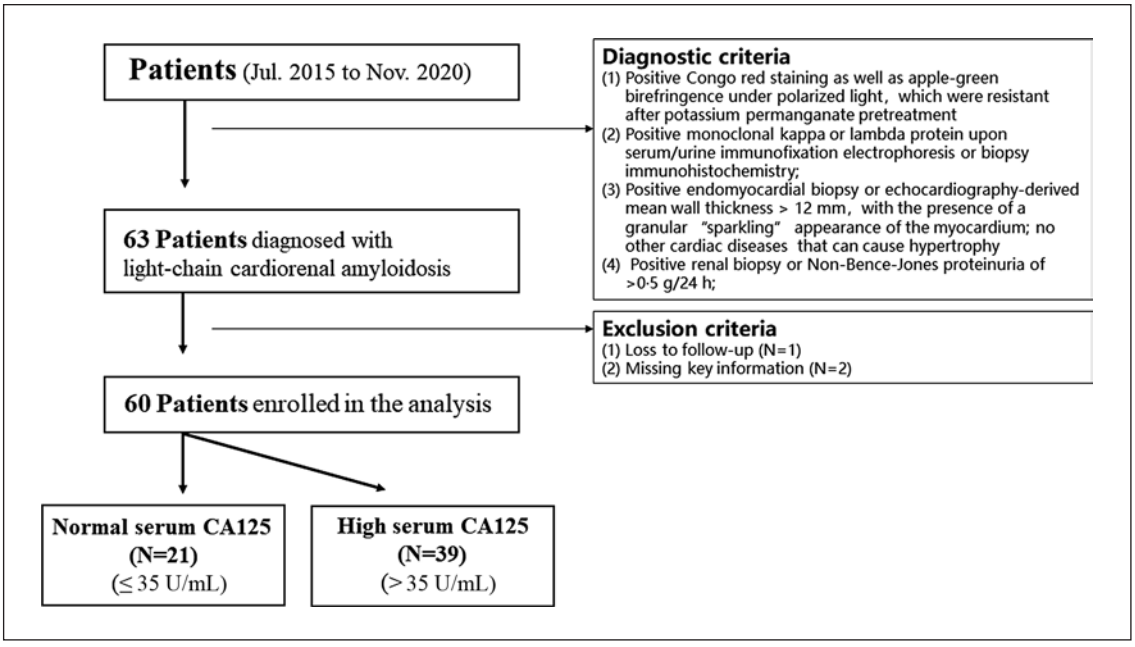

Fig. 1. Flowchart for this retrospective study. CA125, cancer antigen 125.

One patient was lost during follow-up and 2 patients lacked key information. Ultimately, 60 patients were enrolled in the analysis (shown in Fig. 1).

The mean patient age was 61 ± 8 years, and 68% of participants were male. Almost all patients (55/60, 92%) complained of edema or foamy urine at the clinic. Twenty-six (43%) patients were of New York Heart Association (NYHA) class >II. Clinical and echocardiographic characteristics are listed in Table 1. Compared to patients with normal CA125 levels (≤35 U/mL), patients with high CA125 levels (>35 U/mL) had a higher proportion of NYHA class >II cases (56% vs. 19%, $p = 0.005$), pericardial effusion (56% vs. 24%, $p = 0.015$), and edema (74% vs. 43%, $p = 0.016$). In addition, these patients had lower levels of albumin (26.7 ± 8.0 vs. 33.2 ± 7.9 g/L, $p = 0.004$) and LVLS (12.7 ± 3.9 vs. 15.1 ± 2.8%, $p = 0.014$), as well as higher levels of interventricular septal thicknesses (17.6 ± 2.7 vs. 15.9 ± 1.7 mm, $p = 0.012$).

Clinical Characteristics Associated with CA125

Considering that there are fewer reports on CA125 in amyloidosis patients, the present study attempted to identify variables associated with CA125 (online Suppl. Table 1; see www.karger.com/doi/10.1159/000527442 for all online suppl. material). Univariate logistic regression analysis showed that NYHA class >II, pericardial effusion, albumin level, and LVLS may be associated with CA125. A multivariate model incorporating these four variables as well as age showed that age, albumin level, and LVLS were independently associated with CA125 level.

Role of CA125 in Prognostic Analysis

Seventeen (28%) patients died during the follow-up. The median follow-up time was 20 (5–32) months. Kaplan-Meier analysis demonstrated that patients with high CA125 serum levels had a higher risk of all-cause mortality than patients with normal CA125 serum levels, with conservative statistical significance (log-rank $p = 0.051$; Gehan-Breslow-Wilcoxon $p = 0.037$) (shown in Fig. 2). During the long-term follow-up, CA125, estimated glomerular filtration rate (eGFR), E/e', LVEF, LVLS demonstrated the ability to predict prognosis using univariate Cox regression analysis (Table 2). The prognostic potential of CA125 was superior to that of LVEF (C-index 0.685 vs. 0.650), although it was weaker than that of LVLS (C-index 0.685 vs. 0.704). Only a limited correlation was identified between CA125 and other variables (online Suppl. Table 2).

Considering the collinearity between LVEF and LVLS, these two variates were added into two different models. Model 1 including CA125, eGFR, E/e', and LVLS showed acceptable prognostic value (C-index = 0.829, 95% CI: 0.749–0.909) as compared to model 2 in which LVEF was

Table 1. Clinical and echocardiographic characteristics of light-chain cardiorenal amyloidosis

	Normal serum CA125 (≤35 U/mL) *N* = 21	High serum CA125 (>35 U/mL) *N* = 39	*p* value
General characteristics			
Age (years)	58±8	62±8	0.075
Gender (male, %)	15 (71)	26 (67)	0.705
SP (mm Hg)	109±19	108±21	0.839
DP (mm Hg)	71±12	69±14	0.562
NYHA class > II (%)	4 (19)	22 (56)	0.005
Pericardial effusion (%)	5 (24)	22 (56)	0.015
Clinical symptom			
Weak (%)	2 (10)	5 (13)	1.000
Chest distress (%)	2 (10)	7 (18)	0.473
Edema (%)	9 (43)	29 (74)	0.016
Foamy urine (%)	13 (62)	14 (36)	0.053
Laboratory characteristics			
Proteinuria (g/24 h)[a]	2.7±2.3	3.5±2.7	0.273
Albumin (g/L)	33.2±7.9	26.7±8.0	0.004
eGFR (mL/min × 1.73 m^2)	74.3±19.9	68.0±29.1	0.381
CA125 (U/mL)	18.1 (16.4, 25.7)	138.0 (94.4, 419.1)	<0.001
Echocardiographic characteristics			
IVST (mm)	15.9±1.7	17.6±2.7	0.012
PWT (mm)	14.3±2.4	15.8±2.9	0.053
E/e′ (ratio)	14.2±8.6	18.0±7.9	0.087
LVEF (%)	61.0 (59.0, 64.0)	58.0 (51.5, 61.0)	0.077
LVLS (%)	15.1±2.8	12.7±3.9	0.014
Relative apical LVLS (ratio)	0.7 (0.6, 1.0)	0.9 (0.7, 1.2)	0.143

CA125, cancer antigen 125; SP, systolic pressure; DP, diastolic pressure; NYHA class, New York Heart Association class; eGFR, estimated glomerular filtration rate; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVEF, left ventricular ejection fraction; LVLS, left ventricular longitudinal strain. [a] *N* = 58.

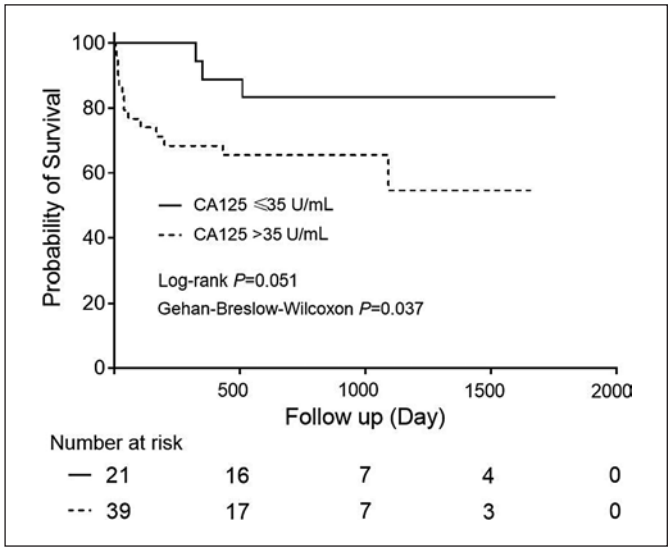

Fig. 2. Kaplan-Meier curves presenting cumulative mortality for patients with different levels of CA125. CA125, cancer antigen 125.

replaced by LVLS (C-index = 0.806, 95% CI: 0.696–0.916). In both two models, CA125 remained an independent prognostic factor (HR = 1.018, 95% CI: 1.005–1.031, p = 0.008 in model 1; HR = 1.020, 95% CI: 1.006–1.033, p = 0.005 in model 2; per 10 U/mL increase) (Table 2). Nested model analysis showed that CA125 provided a significant incremental effect to the risk determined from the remaining three variables (C-index 0.829 vs. 0.784, p = 0.037 in model 1; C-index 0.806 vs. 0.773, p = 0.015 in model 2) (shown in Fig. 3).

Discussion

The present study reported that (1) age, albumin, and LVLS were independently associated with the level of CA125; (2) CA125 was independently associated with the long-term outcome of AL cardiorenal amyloidosis after adjusting for eGFR, E/e', and LV systolic function (LVEF

Table 2. Univariate and multivariate Cox regression analysis to predict long-term outcome

	HR (95% CI)	*p* value	C-index
Univariate			
CA125 (U/mL), per 10 increase	1.014 (1.003,1.026)	0.011	0.685 (0.562, 0.808)
Proteinuria (g/24 h)[a]	1.039 (0.883, 1.222)	0.647	0.472 (0.327, 0.617)
Albumin (g/L)	0.988 (0.934, 1.045)	0.673	0.535 (0.404, 0.666)
eGFR (mL/min × 1.73 m^2)	0.974 (0.956, 0.993)	0.007	0.659 (0.516, 0.802)
E/e' (ratio)	1.072 (1.019, 1.127)	0.007	0.666 (0.543, 0.789)
LVEF (%)	0.929 (0.883, 0.978)	0.005	0.650 (0.507, 0.793)
LVLS (%)	0.839 (0.736, 0.958)	0.009	0.704 (0.567, 0.841)
Model 1			
CA125 (U/mL), per 10 increase	1.018 (1.005, 1.031)	0.008	
eGFR (mL/min × 1.73 m^2)	0.974 (0.953, 0.995)	0.015	
E/e' (ratio)	1.045 (0.979, 1.116)	0.189	
LVEF (%)	0.930 (0.873, 0.990)	0.024	0.829 (0.749, 0.909)
Model 2			
CA125 (U/mL), per 10 increase	1.020 (1.006, 1.033)	0.005	
eGFR (mL/min × 1.73 m^2)	0.972 (0.951, 0.994)	0.012	
E/e' (ratio)	1.058 (0.992, 1.128)	0.085	
LVLS (%)	0.849 (0.745, 0.967)	0.014	0.806 (0.696, 0.916)

Abbreviations are as shown in Table 1. [a] $N = 58$.

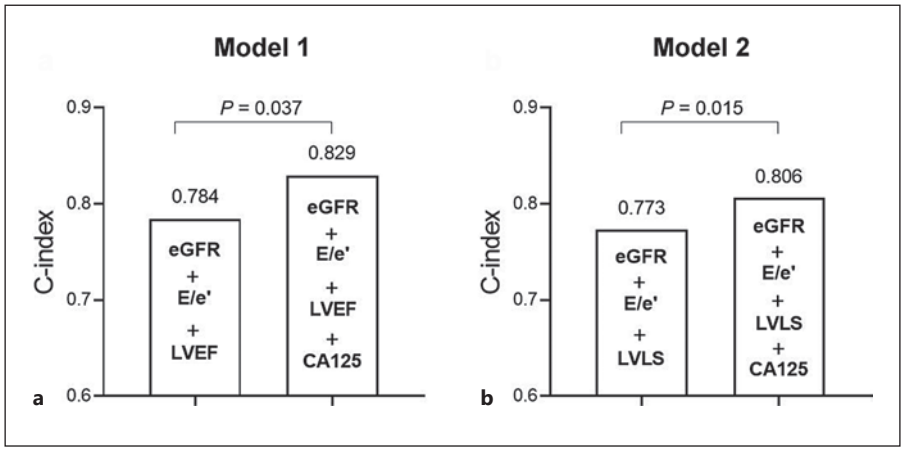

Fig. 3. Incremental prognostic value of CA125 to other three variates. Nested Cox model shows the incremental value of CA125 to eGFR, E/e', and LVEF (**a**) or eGFR, E/e', and LVLS (**b**). CA125, cancer antigen 125; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVLS, left ventricular longitudinal strain.

or LVLS); and (3) CA125 provided a significant incremental effect to the risk determined from variates including eGFR, E/e', and LV systolic function. AL cardiorenal amyloidosis is a common subtype of systemic AL amyloidosis [2] that is classified as one of the main causes of type 5 cardiorenal syndrome [3]. Increased ventricular wall thickness and stiffness lead to diastolic dysfunction, while the loss of urine protein causes decreased colloidal osmotic pressure and hypoproteinemia. Both processes are associated with the increase in peripheral fluid load, which is regarded as one of the prominent features of AL cardiorenal amyloidosis. In addition, nephrogenic symptoms or signs always appear earlier and are more common in this subgroup. More patients turn to the clinic due to edema or foamy urine, which may require the attention of a clinician.

Previous studies have demonstrated the clinical potential of CA125 in heart failure. A multicenter observational study has reported that CA125 was positively and independently associated with the state of congestion in acute heart failure, with efficiency that was superior to that of NT-pro BNP [16]. CA125 has also been regarded as an

indicator guiding diuretic treatment for patients with acute heart failure and renal dysfunction due to its superiority in evaluating fluid overload, higher atrial and pulmonary pressure, and right ventricular dysfunction [12]. Additionally, the increase in CA125 is related to serous cavity effusion [10] and poor prognosis of chronic heart failure [8]. In the present study, age, albumin level, and LVLS were independently associated with CA125. A higher proportion of NYHA class >II cases, pericardial effusion, and edema were reported in patients with high CA125 serum levels. All of these results verified the potential connections between CA125 and fluid overload in AL cardiorenal amyloidosis, while the overload was attributed to the integrated influence of involved organs.

Numerous studies have recognized the satisfactory prognostic value of strain in amyloidosis [17–19], which was consistent with the present results. Univariate analysis demonstrated optimal prognostic potential of LVLS, while the predictive value of CA125 was better than that of LVEF. Interestingly, multivariate analysis including LVEF rather than LVLS showed the better prognostic potential, which may be attributed to the partly overlapping information between CA125 and LVLS. So, the effect of LVLS was weakened in the multivariate model.

A previous research reported by Li et al. [20] had emphasized the increase of CA125 level in AL cardiac amyloidosis patients, which was associated with polyserositis and poor prognosis. Similarly, our study mainly demonstrated the potential association between CA125 and AL cardiorenal amyloidosis, who were more confused by the capacity overload and characterized as the type 5 cardiorenal syndrome. Kaplan-Meier analysis of CA125, using upper normal value (35 U/mL) as the cutoff value, only showed conservative statistical significance. A higher cutoff value may be needed for these specific patients. In addition, an attempt was made to comprehensively assess renal and cardiac systolic and diastolic function using eGFR, E/e', and LVEF or LVLS. CA125 remained an independent prognostic factor and provided incremental information over these variates, showing its potential in prognosis. CA125 itself, as well as the combination with other variates, reflects the clinical value of disease prognosis; further risk stratification based on CA125 is needed in future studies.

Limitation

The limitations of the present study should be acknowledged. Only limited variables were incorporated into the multivariate model due to the small sample size. Prospective studies are needed to verify and improve these results. In addition, a recognized prognostic model using Mayo staging was not described in the study due to the lack of relevant data. However, the levels of BNP and NT-pro BNP were affected by impaired renal function, which inevitably influences the clinical application of this traditional model in AL cardiorenal amyloidosis.

Conclusion

Serum CA125 level was associated with the long-term outcome of AL cardiorenal amyloidosis.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital, Medical School of Zhejiang University and was in accordance with the Declaration of Helsinki, approval number (2020IIT643).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Substantial contributions to conception and design: Bifeng Wu, Jiaran Shi, Jinxiu Yang, and Xingxiang Wang; acquisition of data: Bifeng Wu, Jiaran Shi, Fangcong Yu, Yakui Wu, Xinran Tao, and Tianming Xuan; analysis and interpretation of data: Bifeng Wu and Jiaran Shi; drafting the article: Bifeng Wu, Jinxiu Yang, and Xingxiang Wang; revising it critically for important intellectual content: Jiaran Shi, Fangcong Yu, Yakui Wu, Xinran Tao, and Tianming Xuan; and final approval of the version to be published: all authors.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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