

# CARDIAC CACHEXIA AND CLINICAL OUTCOME OF CHRONIC HEART FAILURE DUE TO RHEUMATIC HEART DISEASE

Evelyn<sup>1</sup>, Andrianto<sup>2</sup>, Mahrus A Rahman<sup>3</sup>

<sup>1</sup>evelyn-2019@fk.unair.ac.id

<sup>1</sup>Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, East Java, Indonesia

<sup>2</sup>Departement of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, East Java, Indonesia

<sup>3</sup>Departement of Pediatric, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, East Java, Indonesia

## Abstract

**Background:** Rheumatic Heart Disease (RHD) is still a significant cause of cardiovascular morbidity and death in developing countries like Indonesia. However, despite being one of the most preventable chronic diseases, RHD still receives less attention, especially in Southeast Asia. PJR that is not treated immediately can develop into chronic heart failure. When heart failure has entered the stage of congestive heart failure, there is activation of a complex network of metabolic, immune, and characteristic neurohormonal factors that can result in cachexia. Cachexia can be an indicator of decreased survival in patients with chronic heart failure due to RHD.

**Objective:** To determine the relationship between cachexia and clinical outcomes of chronic heart failure due to RHD at RSUD Dr. Soetomo.

**Methods:** This study was an analytic observational study using a retrospective cohort design. Data were collected by taking secondary data in the form of patient medical records. There were 106 patients who were taken by non-probability sampling technique. Correlation was determined using Mann-Whitney test and Chi-square test.

**Result:** A total of 106 patients consisted of 53 people with cachexia and 53 people without cachexia, represented both groups dominated by female (57.6%), with largest age range was late adulthood (36-45 years) in both groups (32.1%). Education level data mostly came from secondary schools with a total of 71 people (66.9%) in both groups. The most common type of valve lesion in both groups was mitral stenosis (53.7%). The frequency of hospitalization in patients with cachexia was more frequent with an average of 1.25 times compared to patients without cachexia with an average of 1.02 times. Mortality was higher in patients with cachexia as many as 7 per 53 people (13%) compared to patients without cachexia as many as 3 per 53 people (6%). With Mann-Whitney and chi-square tests, it was found that cachexia had no effect on the hospitalization frequency ( $p=0.453$ ) and mortality ( $p=0.319$ ).

**Conclusion:** Clinical outcomes in chronic heart failure patients due to RHD with cachexia are found to be higher in hospitalization frequency and mortality compared to patients with no cachexia.

Keywords: Cachexia; chronic heart failure; rheumatic heart disease, hospitalization frequency, mortality

## 1. Introduction

Cases of Rheumatic Heart Disease (RHD) globally in 2017 are estimated at 38 million to 40.8 million, with the highest prevalence of disability and death in Oceania, South Asia, and sub-Saharan Africa [25]. A study of a population of mining workers suffering from RHD in Papua found that the incidence

density of RHD was 6.84 per 10,000 people per year. Among these cases, mitral stenosis was the most common valvular lesion at 41% and multivalvular at 6% [36]. Until now, RHD is still a significant cause of cardiovascular morbidity and death in developing countries like Indonesia. However, despite being one of the easiest chronic diseases to prevent, RHD still receives less attention, especially in Southeast Asia. RHD that is not treated immediately can develop into chronic heart failure.

Globally, the greatest burden of valvular disease is valvular heart failure, which is secondary to RHD. In low-income countries, valvular heart failure due to RHD still contributes greatly to morbidity and mortality [42]. In a contemporary cohort study conducted by The Global Rheumatic Heart Disease Registry (the REMEDY study) in 3343 RHD patients, it was found that the majority (63.9%) of patients had moderate to severe multivalvular disease, with complications of congestive heart failure of 33.4% [25].

When heart failure has entered the stage of congestive heart failure, there is activation of a complex network of metabolic, immune, and characteristic neurohormonal factors that result in wasting. This wasting results in a catabolic-anabolic imbalance resulting in nonedematous weight loss which, when certain criteria are met, is known as cachexia. This can be a new problem, because cachexia can cause a decrease in myocardial mass, which can exacerbate existing chronic heart failure. Therefore, patients with cachexia have an extremely poor prognosis, with a mortality rate of up to 50% at 18 months. Cachexia can also be an indicator of decreased survival rate in patients with chronic heart failure, because it can describe the decrease of capacity function and a higher level of heart failure based on the New York Heart Association classification [38].

Based on this background, the purpose of this study is to determine the relationship between cachexia and clinical outcomes of chronic heart failure due to RHD at RSUD Dr. Soetomo. The clinical outcomes consist of hospitalization frequency and mortality. This research was conducted using a sample of outpatients who were diagnosed with chronic heart failure due to RHD at RSUD Dr. Soetomo. With this research, it is hoped that it can increase knowledge and awareness among people with chronic heart failure due to RHD, so that they can pay more attention to nutritional intake and check nutritional status periodically, so that cachexia can be prevented.

## 2. Methods

### 2.1 Study design and site

This study was an analytic observational study using a retrospective cohort design. The research was conducted at RSUD Dr. Soetomo, Surabaya, East Java on September until November 2022.

### 2.2 Sampling and study subject

This study used a non-probability sampling technique with a total sample of 106 people who are suffering from chronic heart failure due to RHD, consisted of 53 people with cachexia and 53 people without cachexia.

### 2.3 Data collection and analysis

The data in this study were collected by taking secondary data in the form of patient medical records, containing the variables to be studied. The variables studied included hospitalization frequency and mortality.

The demographic data consisted of gender, age range, education level, and type of valve lesion. In this study the data obtained will be processed and analyzed using Mann-Whitney test and Chi-square test.

### 3. Result

#### 3.1 Subject characteristic

Based on **Table 1**, it is known that the demographic characteristics of patients with chronic heart failure due to RHD at RSUD Dr. Soetomo Surabaya as many as 53 people with cachexia and 53 people without cachexia, most were female, 27 persons (25.5%) in the cachexia group and 34 persons (32.1%) in the non cachexia group. The age range in patients with chronic heart failure due to RHD was mostly late adulthood (36-45 years old), both in the cachexia group, which was 13 persons (12.3%), and in the non-cachexia group, which was 21 persons (19.8%). Demographic data on education level shows that mostly were secondary education with a total of 33 persons (31.1%) in the cachexia group, and 38 persons (35.8%) in the non cachexia group. The most common type of valve lesion in the cachexia group was mitral stenosis, which was 26 people (24.5%) and mitral regurgitation, which was 26 people (24.5%), while in the non cachexia group, the most common type of valve lesion was mitral stenosis, which was 31 persons (29.2%).

Table 1. Subject characteristics

Characteristics	Cachexia		Non Cachexia	
	Total (n = 53)	Percentage (%)	Total (n = 53)	Percentage (%)
<b>Gender</b>				
Male	26	24,5	19	17,9
Female	27	25,5	34	32,1
<b>Age range</b>				
Toddler (0-5 y.o.)	1	0,9	0	0
Children (5-11 y.o.)	8	7,5	0	0
Early adolescence (12-16 y.o.)	9	8,5	1	0,9
Late adolescence (17-25 y.o.)	2	1,9	4	3,8
Early adulthood (26-35 y.o.)	4	3,8	3	2,8
Late adulthood (36-45 y.o.)	13	12,3	21	19,8
Early elderly (46-55 y.o.)	9	8,5	13	12,3
Late elderly (56-65 y.o.)	5	4,7	10	9,4
Senior (>65 y.o.)	2	1,9	1	0,9
<b>Education level</b>				
Primary education	15	14,2	10	9,4
Secondary education	33	31,1	38	35,8
Advanced education	5	4,7	5	4,7
<b>Type of valve lesion</b>				
Mitral stenosis	26	24,5	31	29,2
Aortic stenosis	1	0,9	1	0,9
Mitral regurgitation	26	24,5	24	22,6

Tricuspid regurgitation	7	6,6	5	4,7
Aortic regurgitation	5	4,7	7	6,6
Mitral prolapse	1	0,9	0	0

### 3.2 Hospitalization frequency

Based on **Table 2**, it is known that the average of hospitalization frequency in the cachexia group was 1.25 times, more often than the average of hospitalization frequency in the non cachexia group which was 1.02 times.

Table 2. Hospitalization frequency

	Mean	
	Cachexia	Non Cachexia
<b>Hospitalization Frequency</b>	1,25	1,02

### 3.3 Mortality

Based on **Table 3**, it is known that in this study, the mortality in the cachexia group was 7 per 53 persons (13%), higher than the mortality in the non cachexia group, which was 3 per 53 persons (6%).

Table 3. Mortality

	Cachexia		Non Cachexia	
	Total (n = 53)	Percentage (%)	Total (n = 53)	Percentage (%)
<b>Mortality</b>				
Yes	7	13	3	6
No	46	87	50	94

## 4. Discussion

### 4.1 Subject Characteristic

#### 4.1.1 Gender

In the cachexia group, there were 26 males (24.5%) and 27 females (25.5%). Meanwhile, in the non-cachexia group, there were 19 males (17.9%) and 34 females (32.1%). The data shows that in the cachexia group, the number of women is greater than in the non cachexia group.

Male have more muscle tissue, while female have more fat deposits [7]. This explains that if there is a wasting of muscle mass, female are more susceptible to more severe cachexia, because they have less muscle mass than men. This also resulted in the average BMI of female being lower than male, both in the

cachexia group (male=17.71 and female=16.96), and the non cachexia group (male=25.31 and female=24.91). This makes the female sex more prone to cachexia.

#### 4.1.2 Age Range

The most age range in patients with chronic heart failure due to rheumatic heart disease was late adulthood (36-45 years), both in the cachexia group, which was 13 persons (12.3%), and in the non-cachexia group, which was 21 persons (19.8%).

This corresponds to the highest age range in rheumatic mitral stenosis patients among mining workers in Papua, Indonesia, which is 35-44 years old [36]. The explanation for this is that, with increasing age, cardiac function decreases, which can exacerbate chronic heart failure due to RHD that has already occurred and makes cachexia more likely to occur [21]. Increasing age also causes progressive dysfunction of organs that affect the ability to maintain homeostasis. In addition, the aging process can lead to an increase in the atherosclerotic process, which can then reduce blood flow to the heart, so that the supply of oxygen to the heart decreases and causes an imbalance between oxygen supply and heart oxygen demand.

#### 4.1.3 Education level

The demographic data of education level for patients with chronic heart failure due to rheumatic heart disease are mostly secondary and primary education. Most education level was secondary education, in the cachexia group there were 33 persons (31.1%), and in the non-cachexia group there were 38 persons (35.8%).

The analysis for this is that patients with a lower level of education tend to go to the medical professional less often for treatment or control when infected with *Streptococcus beta hemolyticus* group A (GAS). This causes delays in early treatment, so that the infection develops into Acute Rheumatic Fever (DRA) and then into Rheumatic Heart Disease (RHD). This is in line with research on the identification and education of adolescents with asthma, where it is said that the level of education is related to the level of control of asthma patients, where patients with lower levels of education tend to control less often [5]. Whereas, public knowledge and awareness of health and disease is a major factor in efforts to prevent RHD and cachexia.

#### 4.1.4 Type of valve lesion

In the cachexia group, the most common type of valve lesion was mitral stenosis, which was 26 persons (24.5%) and mitral regurgitation, which was 26 persons (24.5%). Meanwhile, in the non cachexia group, the most common type of valve lesion was mitral stenosis with 31 persons (29.2%).

This is consistent with a study of a population of miners suffering from RHD in Papua, where mitral stenosis was the most common valvular lesion with a percentage of 41% and multivalvular at 6% [36]. Mean right atrial pressure is usually less than 5 mmHg, while mean left atrial pressure is higher than mean right atrial pressure, but rarely exceeds 8 mmHg. This pressure difference causes the mitral valve in the left heart to be more prone to lesions than other valves [30].

#### 4.2 Hospitalization frequency

In this study, the average frequency of hospitalization in the cachexia group was 1.25 times. Meanwhile, the average frequency of hospitalization in the non-cachexia group was 1.02 times. The average frequency of hospitalization in the cachexia group was more often than that in the non cachexia group.

The higher frequency of hospitalization in patients with chronic heart failure due to RHD in the cachexia group is in line with a study where valvular heart failure due to RHD still contributes greatly to morbidity, one of which is the frequency of hospitalization [42]. This is because apart from skeletal muscle, wasting also occurs in the myocardium as shown in a clinical study comparing left ventricular masses of cachectic and non-cachectic patients using MRI [6] [38]. This decrease in myocardial mass will have an impact on reducing the ability and effectiveness of the heart's work, which then worsens the existing clinical outcomes, which can result in patients being hospitalized more often.

Based on medical record data observed by researchers, patients with chronic heart failure due to RHD showed that the majority of patients at RSUD Dr. Soetomo routinely controls once a month. This of course can improve the patient's health status, thus causing the patient's hospitalization frequency to be lower [40]. Therefore, it can be said that routine control can improve the patient's health status.

#### 4.3 Mortality

In this study, the mortality in the cachexia group was 7 per 53 persons (13%), while the mortality rate in the non cachexia group was 3 per 53 persons (6%). This shows that the mortality for any cause (all cause mortality) in the cachexia group is higher than the non cachexia group.

Cachexia in some chronic diseases strongly predicts increased mortality, and contributes to the reduced quality of life that accompanies end-stage disease. These results are in line with research about explanation of heart failure hyper-mortality in sub-Saharan Africa, where cachexia causes HFrEF and higher mortality [22]. Mortality of patients with chronic heart failure due to RHD with cachexia is higher than that without cachexia, indicating that patients with cachexia have a very poor prognosis.

Based on medical record data, it can be seen that the majority of PJR patients at RSUD Dr. Soetomo routine control once a month. This certainly affects the patient's condition as a whole where the more routine the patient is in control, the lower the mortality. This is in line with a study where it can be concluded that routine control can improve health status and reduce mortality [40].

#### 5. Conclusion

In this study it is known that cachexia results in a higher frequency of hospitalization and mortality in patients with chronic heart failure due to RHD.

#### Acknowledgements

The author would like to thank the Faculty of Medicine, Airlangga University and RSUD Dr. Soetomo, Surabaya for contributing and supporting the process of completing this study.

#### References

- [1] Barazzoni, R, Gortan Cappellari, G, Palus, S, Vinci, P, Ruozzi, G, Zanetti, M, Semolic, A, Ebner, N, von Haehling, S, & Sinagra, G, 2017, 'Acylated ghrelin treatment normalizes skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rat chronic heart failure', *Journal of Cachexia, Sarcopenia and Muscle*, vol. 8, no. 6, pp. 991–998.
- [2] Carapetis, JR, 2007, 'Rheumatic Heart Disease in Developing Countries', *New England Journal of Medicine*, vol. 357, no. 5, pp. 439–441, doi: 10.1056/NEJMp078039.
- [3] Carapetis, JR, Beaton, A, Cunningham, MW, Guilherme, L, Karthikeyan, G, Mayosi, BM, Sable, C, Steer, A, Wilson, N, Wyber,

- R, & Zühlke, L, 2016, 'Acute rheumatic fever and rheumatic heart disease', *Nature Reviews. Disease Primers*, vol. 2, p. 15084, doi: 10.1038/nrdp.2015.84.
- [4] Cunningham, MW, 2000, 'Pathogenesis of group A streptococcal infections', *Clinical Microbiology Reviews*, vol. 13, no. 3, pp. 470–511, doi: 10.1128/CMR.13.3.470.
- [5] Davis, A, Savage Brown, A, Edelstein, J, & Tager, IB, 2008, 'Identification and education of adolescents with asthma in an urban school district: results from a large-scale asthma intervention', *Journal of Urban Health*, vol. 85, no. 3, pp. 361–374.
- [6] Florea, VG, Moon, J, Pennell, DJ, Doehner, W, Coats, AJS, & Anker, SD, 2004, 'Wasting of the left ventricle in patients with cardiac cachexia: a cardiovascular magnetic resonance study', *International Journal of Cardiology*, vol. 97, no. 1, pp. 15–20.
- [7] Folland, JP & Williams, AG, 2007, 'Morphological and neurological contributions to increased strength', *Sports Medicine*, vol. 37, no. 2, pp. 145–168.
- [8] Barazzoni, R, Gortan Cappellari, G, Palus, S, Vinci, P, Ruozzi, G, Zanetti, M, Semolic, A, Ebner, N, von Haehling, S, & Sinagra, G, 2017, 'Acylated ghrelin treatment normalizes skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rat chronic heart failure', *Journal of Cachexia, Sarcopenia and Muscle*, vol. 8, no. 6, pp. 991–998.
- [9] Carapetis, JR, 2007, 'Rheumatic Heart Disease in Developing Countries', *New England Journal of Medicine*, vol. 357, no. 5, pp. 439–441, doi: 10.1056/NEJMp078039.
- [10] Carapetis, JR, Beaton, A, Cunningham, MW, Guilherme, L, Karthikeyan, G, Mayosi, BM, Sable, C, Steer, A, Wilson, N, Wyber, R, & Zühlke, L, 2016, 'Acute rheumatic fever and rheumatic heart disease', *Nature Reviews. Disease Primers*, vol. 2, p. 15084, doi: 10.1038/nrdp.2015.84.
- [11] Cunningham, MW, 2000, 'Pathogenesis of group A streptococcal infections', *Clinical Microbiology Reviews*, vol. 13, no. 3, pp. 470–511, doi: 10.1128/CMR.13.3.470.
- [12] Davis, A, Savage Brown, A, Edelstein, J, & Tager, IB, 2008, 'Identification and education of adolescents with asthma in an urban school district: results from a large-scale asthma intervention', *Journal of Urban Health*, vol. 85, no. 3, pp. 361–374.
- [13] Florea, VG, Moon, J, Pennell, DJ, Doehner, W, Coats, AJS, & Anker, SD, 2004, 'Wasting of the left ventricle in patients with cardiac cachexia: a cardiovascular magnetic resonance study', *International Journal of Cardiology*, vol. 97, no. 1, pp. 15–20.
- [14] Folland, JP & Williams, AG, 2007, 'Morphological and neurological contributions to increased strength', *Sports Medicine*, vol. 37, no. 2, pp. 145–168.
- [15] Galvin, JE, Hemric, ME, Ward, K, & Cunningham, MW, 2000, 'Cytotoxic mAb from rheumatic carditis recognizes heart valves and laminin.', *The Journal of Clinical Investigation*, vol. 106, no. 2, pp. 217–224, doi: 10.1172/JCI7132.
- [16] Gewitz, MH, Baltimore, RS, Tani, LY, Sable, CA, Shulman, ST, Carapetis, J, Remenyi, B, Taubert, KA, Bolger, AF, Beerman, L, Mayosi, BM, Beaton, A, Pandian, NG, & Kaplan, EL, 2015, 'Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography a scientific statement from the American heart association', *Circulation*, vol. 131, no. 20, pp. 1806–1818, doi: 10.1161/CIR.0000000000000205.
- [17] Griva, M, 2016, 'Cardiac cachexia – Up-to-date 2015', *Cor et Vasa*, vol. 58, no. 4, pp. e431–e438, doi: <https://doi.org/10.1016/j.crvasa.2015.08.003>.
- [18] Guilherme, L, Cury, P, Demarchi, LMF, Coelho, V, Abel, L, Lopez, AP, Oshiro, SE, Aliotti, S, Cunha-Neto, E, Pomerantzeff, PMA, Tanaka, AC, & Kalil, J, 2004, 'Rheumatic heart disease: proinflammatory cytokines play a role in the progression and maintenance of valvular lesions.', *The American Journal of Pathology*, vol. 165, no. 5, pp. 1583–1591, doi: 10.1016/S0002-9440(10)63415-3.
- [19] Guilherme, L, Kalil, J, & Cunningham, M, 2006, 'Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease', *Autoimmunity*, vol. 39, no. 1, pp. 31–39.
- [20] Habedank, D, Meyer, FJ, Hetzer, R, Anker, SD, & Ewert, R, 2013, 'Relation of respiratory muscle strength, cachexia and survival in severe chronic heart failure.', *Journal of Cachexia, Sarcopenia and Muscle*, vol. 4, no. 4, pp. 277–285, doi: 10.1007/s13539-013-0109-7.
- [21] Harigustian, Y, Dewi, A, & Khoiriyati, A, 2016, 'Gambaran Karakteristik Pasien Gagal Jantung Usia 45–65 Tahun di Rumah Sakit Pku Muhammadiyah Gamping Sleman', *IJNP (Indonesian Journal of Nursing Practices)*, vol. 1, no. 1, pp. 55–60.
- [22] Joshi, A V., D'Souza, AO, & Madhavan, SS, 2004, 'Differences in hospital length-of-stay, charges, and mortality in congestive heart failure patients.', *Congestive Heart Failure (Greenwich, Conn.)*, vol. 10, no. 2, pp. 76–84, doi: 10.1111/j.1527-5299.2004.02008.x.
- [23] King, D, Smith, ML, Chapman, TJ, Stockdale, HR, & Lye, M, 1996, 'Fat malabsorption in elderly patients with cardiac cachexia', *Age and Ageing*, vol. 25, no. 2, pp. 144–149.
- [24] Krysztofiak, H, Wleklík, M, Migaj, J, Dudek, M, Uchmanowicz, I, Lisiak, M, Kubiela, G, Straburzyńska-Migaj, E, Lesiak, M, & Kałużna-Oleksy, M, 2020, 'Cardiac Cachexia: A Well-Known but Challenging Complication of Heart Failure.', *Clinical Interventions in Aging*, vol. 15, pp. 2041–2051, doi: 10.2147/CIA.S273967.



- [25] Kumar, RK, Antunes, MJ, Beaton, A, Mirabel, M, Nkomo, VT, Okello, E, Regmi, PR, Reményi, B, Sliwa-Hähnle, K, Zühlke, LJ, & Sable, C, 2020, 'Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap: A Scientific Statement From the American Heart Association.', *Circulation*, vol. 142, no. 20, pp. e337–e357, doi: 10.1161/CIR.0000000000000921.
- [26] Madiyono, B, Sastroasmoro, S, Oesman, IN, Putra, ST, & Advani, N, 1994, 'Diagnosis of Rheumatic Fever: Which Modification?', *Paediatrica Indonesiana*, vol. 34, no. 5–6, pp. 141–148.
- [27] Mangner, N, Matsuo, Y, Schuler, G, & Adams, V, 2013, 'Cachexia in chronic heart failure: endocrine determinants and treatment perspectives.', *Endocrine*, vol. 43, no. 2, pp. 253–265, doi: 10.1007/s12020-012-9767-z.
- [28] Marijon, E, Mirabel, M, Celermajer, DS, & Jouven, X, 2012, 'Rheumatic heart disease', *The Lancet*, vol. 379, no. 9819, pp. 953–964.
- [29] Mariyono, HH & Santoso, A, 2007, 'Gagal jantung', *J Peny Dalam*, vol. 8, no. 3, pp. 85–94.
- [30] Miller-Hance, WC & Gertler, R, 2019, 'Essentials of Cardiology', in *A Practice of Anesthesia for Infants and Children*, pp. 355–392, Elsevier.
- [31] Noubiap, JJ, Agbor, VN, Bigna, JJ, Kaze, AD, Nyaga, UF, & Mayosi, BM, 2019, 'Prevalence and progression of rheumatic heart disease: a global systematic review and meta-analysis of population-based echocardiographic studies', *Scientific Reports*, vol. 9, no. 1, p. 17022, doi: 10.1038/s41598-019-53540-4.
- [32] PERKI, 2016, 'Panduan Praktik Klinis (PPK) dan Clinical Pathway (CP) Penyakit Jantung dan Pembuluh Darah', *Jurnal Kardiologi Indonesia*, pp. 216–218.
- [33] PERKI, 2020, 'Pedoman Tatalaksana Gagal Jantung', *Jurnal Kardiologi Indonesia*, pp. 22–25.
- [34] Ponikowski, P, Voors, AA, Anker, SD, Bueno, H, Cleland, JGF, Coats, AJS, Falk, V, González-Juanatey, JR, Harjola, V-P, & Jankowska, EA, 2016, '2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure', *Kardiologia Polska (Polish Heart Journal)*, vol. 74, no. 10, pp. 1037–1147.
- [35] Roberts, S, Kosanke, S, Dunn, ST, Jankelow, D, Duran, CMG, & Cunningham, MW, 2001, 'Pathogenic mechanisms in rheumatic carditis: focus on valvular endothelium', *The Journal of Infectious Diseases*, vol. 183, no. 3, pp. 507–511.
- [36] Rodriguez-Fernandez, R, Amiya, R, Wyber, R, Widdodow, W, & Carapetis, J, 2015, 'Rheumatic heart disease among adults in a mining community of Papua, Indonesia: findings from an occupational cohort.', *Heart Asia*, vol. 7, no. 2, pp. 44–48, doi: 10.1136/heartasia-2015-010641.
- [37] Suzuki, H, Asakawa, A, Amitani, H, Nakamura, N, & Inui, A, 2013, 'Cancer cachexia—pathophysiology and management', *Journal of Gastroenterology*, vol. 48, no. 5, pp. 574–594.
- [38] Valentova, M, Anker, SD, & von Haehling, S, 2020, 'Cardiac Cachexia Revisited: The Role of Wasting in Heart Failure.', *Heart Failure Clinics*, vol. 16, no. 1, pp. 61–69, doi: 10.1016/j.hfc.2019.08.006.
- [39] Veasy, LG & Tani, LY, 2005, 'A new look at acute rheumatic mitral regurgitation', *Cardiology in the Young*, vol. 15, no. 6, pp. 568–577.
- [40] Wasson, J, Gaudette, C, Whaley, F, Sauvigne, A, Baribeau, P, & Welch, HG, 1992, 'Telephone care as a substitute for routine clinic follow-up', *Jama*, vol. 267, no. 13, pp. 1788–1793.
- [41] WHO Study Group on Rheumatic Fever and Rheumatic Heart Disease (2001 : Geneva, S & Organization, WH, 2004, 'Rheumatic fever and rheumatic heart disease : report of a WHO expert consultation, Geneva, 20 October - 1 November 2001', *World Health Organization, Geneva PP - Geneva*, Retrieved from <https://apps.who.int/iris/handle/10665/42898>.
- [42] Ziaecian, B & Fonarow, GC, 2016, 'Epidemiology and aetiology of heart failure.', *Nature Reviews. Cardiology*, vol. 13, no. 6, pp. 368–378, doi: 10.1038/nrcardio.2016.25.