E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.01.315

Research Article

HABITUAL TODDY INTAKE AS A POTENTIAL RISK FACTOR FOR RIGHT VENTRICULAR FAILURE

Dr. Yasmeen Chand Patel[1], Dr. Mastan Pathan[2], Dr. D Priya[3], Dr Sree Harsha Dasari[4], Dr. Smita Deokar[5]*

[1]Associate Professor, Dept of General Medicine, Arundhati Institute of Medical Sciences, Hyderabad, Telangana, India.
[2]Assistant Professor, Dept of Gen Surgery, Arundhati Institute of Medical Sciences, Hyderabad, Telangana, India
[3]Assistant Professor, Dept of Pulmonology, Arundhati Institute of Medical Sciences, Hyderabad, Telangana, India.
[4]Medical officer, Dept of General Medicine, Arundhati Institute of Medical Sciences, Hyderabad, Telangana, India.
[5]Professor(Addl), Dept of Biochemistry, HBT Medical College and Dr. RN Cooper Municipal General Hospital, Juhu, Mumbai, Maharashtra, India.
***Corresponding author: Dr. Smita Deokar,** Professor (Addl), Dept of Biochemistry, HBT Medical College and Dr RN Cooper Municipal General Hospital, Juhu, Mumbai, Maharashtra, India.
Email id – smitapawar83@gmail.com

Abstract

Background: Right ventricular failure is a serious clinical condition commonly associated with pulmonary hypertension, chronic lung disease, and other cardiopulmonary disorders.

Objective: To evaluate habitual toddy intake as a potential risk factor for right ventricular failure and to assess its association with demographic, clinical, laboratory, pulmonary, and echocardiographic characteristics.

Methodology: This was a cross-sectional analytical study conducted at Arundhati Institute of Medical Sciences, Hyderabad, Telngana, India from Nov 2023 to June 2024. A total of 40 patients with echocardiographic evidence of right atrial and right ventricular dilatation and clinical features suggestive of right ventricular failure were included.

Results: The mean age of the patients was 57.40 ± 13.48 years, and males constituted 52.5% of the study population. The most common presenting features were exercise limitation in 34 (85.0%) patients, bilateral pedal edema in 28 (70.0%), fatigue in 18 (45.0%), and abdominal distension in 13 (32.5%). Habitual toddy intake was present in 17 (42.5%) patients, making it the most frequent risk factor, followed by COPD in 14 (35.9%), smoking in 12 (30.0%), and alcohol intake in 9 (23.7%). Mean oxygen saturation was 83.38 ± 13.32%, mean PaO_2 was 73.28 ± 12.96 mmHg, and mean RVSP was 70.68 ± 23.31 mmHg, while mean LVEF remained preserved at 60.98 ± 1.21%.

Conclusion: Habitual toddy intake was frequent among patients with right ventricular failure and may be an important, underrecognized potential risk factor.

Keywords: Toddy intake, right ventricular failure, pulmonary hypertension, COPD, alcohol exposure, tricuspid regurgitation.

INTRODUCTION

The relationship between alcohol consumption and cardiovascular diseases (CVD), the number one cause of death in the world [1], has been controversial. The epidemiologic association of light to moderate alcohol use and reduced CVD risk has been consistently demonstrated in observational studies, with other associations being either J- or U-shaped [2]. The beneficial effects of alcohol observed on the heart, however, have been attributed to residual confounding due to positive lifestyle, socioeconomic and behavioral factors that are likely to be associated with light drinking [3]. Right ventricular failure is a clinically important condition which occurs when the right ventricle fails to generate sufficient forward flow through the pulmonary circulation leading to systemic venous congestion, decreased exercise tolerance, peripheral edema, abdominal distention, and progressive functional impairment. Right ventricular failure in most patients is not an isolated myocardial disease, but a result of chronic pressure overload either from pulmonary hypertension or chronic lung disease, pulmonary vascular disease or advanced hepatic and cardiopulmonary disease. The right ventricle suffers from increased afterload stress as a result of sustained increments in pulmonary vascular resistance and is thinned and less tolerant of increases in afterload stress than is the left ventricle; thus, sustained increases in pulmonary vascular resistance can cause right ventricular dilatation, tricuspid regurgitation and eventual decompensation. Therefore, right ventricular failure is an important factor in the morbidity and outcome of patients with cardiopulmonary disease [4].

It is well established that alcohol consumption is an important risk factor for cardiovascular damage. Although alcohol-related dilated cardiomyopathy, myocardial dysfunction and systemic hypertension have traditionally been linked to chronic alcohol exposure, there is no restriction on the left ventricle [5]. Experimental and clinical findings have also shown that chronic alcohol use can have a direct effect on the pulmonary vasculature and right heart through the development of myocardial toxicity, or indirect effects through liver disease, portal hypertension, nutritional deficiency and concurrent smoking-related lung injury. In particular, portal hypertension can be a risk factor for the development of portopulmonary hypertension which is an elevated right ventricular afterload and may progress to right heart failure [6]. In patients with advanced liver disease, POH has shown to be an important complication and poor prognostic factor. One of these exposures is the use of alcohol. Myocardial toxicity and development of alcohol related cardiomyopathy (ARC), a non-ischemic dilated cardiomyopathy, associated with prolonged heavy drinking, has long been linked to chronic alcoholism [7]. Current literature also records that alcohol-related cardiomyopathy rarely occurs in isolation and often patients also suffer from other conditions such as the presence of atrial arrhythmias, cigarette smoking, metabolic or hepatic comorbidities, and hypertension. That's important because the cardiovascular system can be injured by various and overlapping pathways, and alcohol's mechanism of action is not necessarily a straightforward one. These factors, such as chronic lung disease, inadequate nutrition,

liver dysfunction and systemic inflammation can compound the effect of alcohol on the pulmonary vascular stress and right ventricular load in real world patients [8].

This association between alcohol and right ventricular failure may then have a direct and indirect link [9]. Ethanol exposure can directly cause myocardial remodeling and decreased ventricular reserve. Alcohol-related liver injury can also cause portal hypertension, which can cause portopulmonary hypertension, a known type of pulmonary arterial hypertension, which can lead to right heart failure [10]. New reviews define portopulmonary hypertension as a significant pulmonary vascular event of portal hypertension with clinical implications for exercise capacity, transplant candidacy and mortality. That is, a chronic alcoholic patient may not have to develop classic left-sided alcoholic cardiomyopathy before developing right ventricular failure; the liver–lung–heart axis may be sufficient to cause the right-sided failure in an alcoholic [11]. It is a traditional fermented beverage known locally as "toddy", or palm wine, or palm toddy, that is traditionally consumed in several tropical and South Asian communities [12]. It is made from palm sap and is naturally fermented quickly, which makes it an alcoholic beverage of varying alcohol content depending on the time, fermentation conditions and storage. Toddys are said to be a mildly to moderately alcoholic beverage with a typical alcohol content of about 3% to 6%, but may vary significantly depending on the local context. The consumption of toddy has been noted as being culturally acceptable and produced in an informal way, hence, it is possible that although persons are exposed to ethanol and other fermentation related compounds for a prolonged period of time, it may be unreported as part of routine history taking.

Objective

To evaluate habitual toddy intake as a potential risk factor for right ventricular failure and to assess its association with demographic, clinical, laboratory, pulmonary, and echocardiographic characteristics.

METHODOLOGY

This was a cross-sectional analytical study conducted at Arundhati Institute of Medical Sciences, Hyderabad, Telngana, India from Nov 2023 to June 2024. A total of 40 patients with echocardiographic evidence of right atrial and right ventricular dilatation and clinical features suggestive of right ventricular failure were included.

Inclusion Criteria

Patients aged 18 years and above, of either gender, presenting with clinical features of right ventricular failure such as dyspnea, pedal edema, abdominal distension, or exercise limitation were included in the study. Patients were required to have echocardiographic evidence of right atrial and right ventricular dilatation, with or without elevated right ventricular systolic pressure, and only those willing to participate and provide informed consent were enrolled.

Exclusion Criteria

Patients with known congenital heart disease, established left ventricular systolic

failure as the primary cause of symptoms, or significant rheumatic or structural valvular heart disease causing secondary right heart involvement were excluded from the study. Patients with incomplete clinical, echocardiographic, or exposure data, as well as those unwilling to participate, were also excluded.

Data Collection Procedure

After approval from the institutional ethical review board, eligible patients presenting to the study setting were recruited through non-probability consecutive sampling. Written informed consent was obtained from all participants before enrollment. A structured proforma was used to collect information regarding demographic characteristics, presenting complaints, smoking status, habitual toddy intake, alcohol use, and relevant comorbid conditions including previous history of COVID-19, tuberculosis, chronic obstructive pulmonary disease, chronic kidney disease, cirrhosis with portal hypertension, obstructive sleep apnea, connective tissue disease, and previous deep vein thrombosis. Habitual toddy intake was assessed on history and was defined as regular consumption of toddy over a prolonged period as reported by the patient. Clinical examination findings including blood pressure, pulse rate, oxygen saturation, and signs of right ventricular failure were documented. Investigations including arterial blood gas analysis, pulmonary function tests, HRCT chest findings, and echocardiographic parameters such as left atrial diameter, right atrial area, right ventricular systolic pressure, left ventricular ejection fraction, tricuspid regurgitation severity, pericardial effusion, and associated valvular lesions were recorded for analysis.

Statistical Analysis

Data were entered and analyzed using SPSS version 26. Quantitative variables such as age, blood pressure, pulse rate, oxygen saturation, arterial blood gas values, pulmonary function test results, and echocardiographic measurements were presented as mean ± standard deviation or median with interquartile range where appropriate. Qualitative variables such as gender, habitual toddy intake, smoking, comorbidities, HRCT findings, right ventricular systolic pressure categories, and tricuspid regurgitation severity were expressed as frequency and percentage. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The mean age was 57.40 ± 13.48 years, and most patients were aged 40–59 years or ≥60 years, with 17 (42.5%) in each group. Males were slightly more frequent than females, 21 (52.5%) versus 19 (47.5%). Most patients had NYHA grade 2 dyspnea, seen in 21 (52.5%), followed by grade 3 in 15 (37.5%). Exercise limitation was the commonest symptom, present in 34 (85.0%) patients, followed by bilateral pedal edema in 28 (70.0%), fatigue in 18 (45.0%), and abdominal distension in 13 (32.5%).

Table 1. Baseline demographic characteristics and presenting symptoms of the study population (N = 40)

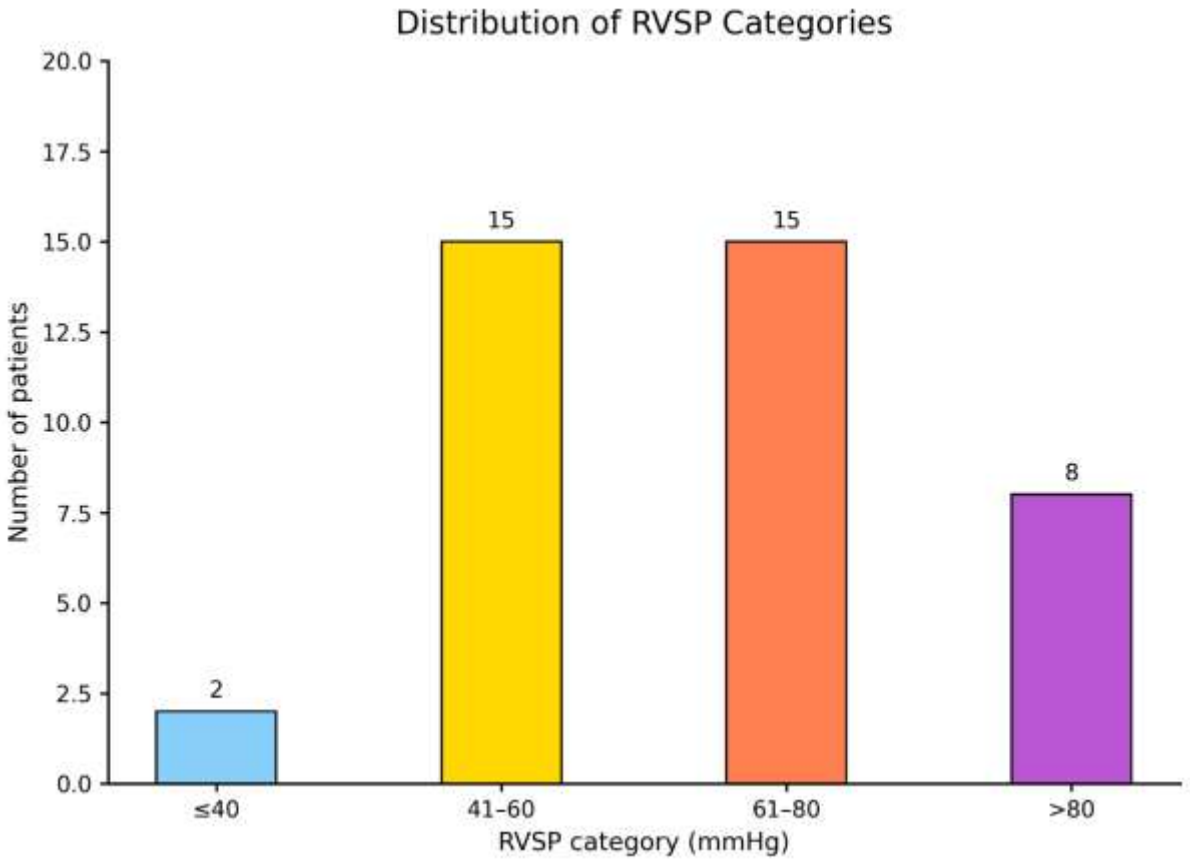
Variable	n (%) / Mean ± SD

Age (years)	57.40 ± 13.48
<40 years	6 (15.0)
40–59 years	17 (42.5)
≥60 years	17 (42.5)
Sex	
Male	21 (52.5)
Female	19 (47.5)
Shortness of breath (NYHA grade)	
Grade 1	3 (7.5)
Grade 2	21 (52.5)
Grade 3	15 (37.5)
Grade 4	1 (2.5)
Fatigue	18 (45.0)
Abdominal distension	13 (32.5)
Bilateral pedal edema	28 (70.0)
Exercise limitation	34 (85.0)
Cardiac angina	0 (0.0)
Syncope	0 (0.0)
Family history of similar illness	1 (2.5)

Habitual toddy intake was the most common risk factor, reported in 17 (42.5%) patients, followed by COPD in 14 (35.9%) and smoking in 12 (30.0%). Alcohol intake was present in 9 (23.7%), previous COVID-19 in 5 (12.8%), and cirrhosis with portal hypertension in 5 (12.5%) patients.

Table 2. Past history, risk factors, and comorbid conditions

Variable	n (%)
Previous history of COVID-19	5 (12.8)
Previous history of tuberculosis	2 (5.0)
Smoker	12 (30.0)
Habitual toddy intake	17 (42.5)
Alcohol intake	9 (23.7)
COPD	14 (35.9)
Chula worker	1 (2.5)
Connective tissue disease	1 (2.5)
Prior diagnosed DVT	1 (2.5)
Hemoptysis	0 (0.0)
HIV	0 (0.0)
Obstructive sleep apnea	1 (2.5)
CKD	3 (7.9)
Cirrhosis with portal hypertension	5 (12.5)



The mean systolic and diastolic blood pressures were 132.44 ± 16.58 mmHg and 74.72 ± 12.01 mmHg, while pulse rate was 90.52 ± 16.15 beats/min. Mean oxygen saturation was low at 83.38 ± 13.32%, with ABG values showing pH 7.31 ± 0.12, PaO2 73.28 ± 12.96 mmHg, and PaCO2 46.00 ± 11.07 mmHg. Pulmonary function showed mean FEV1 of 65.38 ± 22.30, FVC of 79.95 ± 16.38, and FEV1/FVC of 77.28 ± 19.23. Echocardiography showed raised RVSP at 70.68 ± 23.31 mmHg with preserved LVEF of 60.98 ± 1.21%.

Table 3. Clinical, arterial blood gas, pulmonary function, and echocardiographic continuous parameters

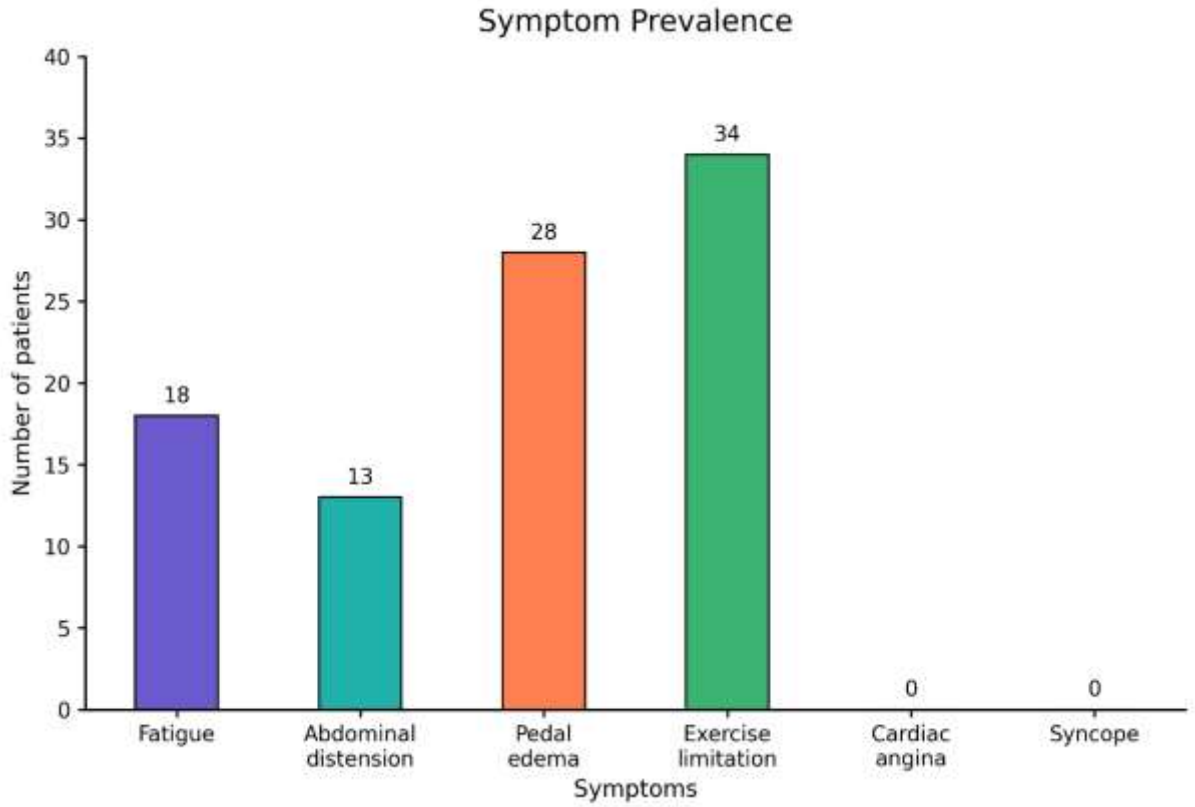
Variable	n	Mean ± SD	Range
Age (years)	40	57.40 ± 13.48	28–85
Systolic blood pressure (mmHg)	39	132.44 ± 16.58	110–184
Diastolic blood pressure (mmHg)	39	74.72 ± 12.01	52–117
Pulse rate (beats/min)	40	90.52 ± 16.15	67–170
SpO2 (%)	40	83.38 ± 13.32	52–99
ABG pH	40	7.31 ± 0.12	7.1–7.5
ABG PaO2(mmHg)	40	73.28 ± 12.96	50–99
ABG PaCO2 (mmHg)	40	46.00 ± 11.07	23–70
PFT FEV2	40	65.38 ± 22.30	23–105
PFT FVC	40	79.95 ± 16.38	45–110
PFT FEV2/FVC	40	77.28 ± 19.23	34–111
LA diameter (cm)	40	3.22 ± 0.33	2.7–4.6

RA area (cm)	24	4.45 ± 0.42	3.5–5.1
RVSP (mmHg)	40	70.68 ± 23.31	40–126
LVEF (%)	40	60.98 ± 1.21	60–65

On HRCT, normal findings were seen in 10 (25.0%) patients, while emphysematous changes were present in 9 (22.5%) and cardiomegaly with pulmonary artery dilatation in 8 (20.0%). Most patients had elevated RVSP, with 15 (37.5%) each in the 41–60 mmHg and 61–80 mmHg categories, while 8 (20.0%) had RVSP >80 mmHg. Tricuspid regurgitation was mild in 15 (37.5%), moderate in 11 (27.5%), and severe in 13 (32.5%).

Table 4. HRCT and echocardiographic categorical findings

Variable	n (%)
HRCT findings	
Normal study	10 (25.0)
Emphysematous changes	9 (22.5)
Emphysematous with fibrotic/interstitial changes	2 (5.0)
Cardiomegaly with emphysematous changes	4 (10.0)
Cardiomegaly / pulmonary artery dilatation	8 (20.0)
Cardiomegaly with fibrotic changes	1 (2.5)
Fibrotic/interstitial changes	2 (5.0)
Pleural effusion	2 (5.0)
Bronchiectatic changes	1 (2.5)
Other findings	1 (2.5)
RVSP category	
≤40 mmHg	2 (5.0)
41–60 mmHg	15 (37.5)
61–80 mmHg	15 (37.5)
>80 mmHg	8 (20.0)
Tricuspid regurgitation severity	
Trivial TR	1 (2.5)
Mild TR	15 (37.5)
Moderate TR	11 (27.5)
Severe TR	13 (32.5)
Pericardial effusion	5 (12.5)
Associated valvular lesions	
None	33 (82.5)
Trivial MR	4 (10.0)
Mild MR	3 (7.5)



Smoking was significantly more common in males, seen in 12 (57.1%) men and no females (p<0.001), while alcohol intake was also limited to males, affecting 9 (47.4%) men (p=0.001). COPD was more frequent in males than females, 12 (57.1%) versus 2 (11.1%) (p=0.008), and cirrhosis with portal hypertension was also higher in males, 5 (23.8%) versus none in females (p=0.049). Overall, males showed a greater burden of risk factors, while symptoms and cardiac findings were largely similar between sexes.

Table 5. Sex-wise comparison of categorical variables

Variable	Female n (%)	Male n (%)	p-value
Age group			0.172
<40 years	2 (10.5)	4 (19.0)	
40–59 years	6 (31.6)	11 (52.4)	
≥60 years	11 (57.9)	6 (28.6)	
NYHA grade			0.387
Grade 1	1 (5.3)	2 (9.5)	
Grade 2	8 (42.1)	13 (61.9)	
Grade 3	9 (47.4)	6 (28.6)	
Grade 4	1 (5.3)	0 (0.0)	
Fatigue	9 (47.4)	9 (42.9)	1.000
Abdominal distension	4 (21.1)	9 (42.9)	0.258
Bilateral pedal edema	12 (63.2)	16 (76.2)	0.580
Exercise limitation	15 (78.9)	19 (90.5)	0.398
Family history of similar	1 (5.3)	0 (0.0)	0.475

illness			
Previous history of COVID-19	1 (5.6)	4 (19.0)	0.342
Previous history of tuberculosis	2 (10.5)	0 (0.0)	0.219
Smoker	0 (0.0)	12 (57.1)	<0.001
Habitual toddy intake	8 (42.1)	9 (42.9)	0.785
Alcohol intake	0 (0.0)	9 (47.4)	0.001
COPD	2 (11.1)	12 (57.1)	0.008
CKD	1 (5.9)	2 (9.5)	1.000
Cirrhosis with portal hypertension	0 (0.0)	5 (23.8)	0.049
Pericardial effusion	2 (10.5)	3 (14.3)	1.000
RVSP category			0.197
≤40 mmHg	0 (0.0)	2 (9.5)	
41–60 mmHg	8 (42.1)	7 (33.3)	
61–80 mmHg	9 (47.4)	6 (28.6)	
>80 mmHg	2 (10.5)	6 (28.6)	
Tricuspid regurgitation severity			0.768
Trivial TR	1 (5.3)	0 (0.0)	
Mild TR	8 (42.1)	7 (33.3)	
Moderate TR	5 (26.3)	6 (28.6)	
Severe TR	5 (26.3)	8 (38.1)	
Associated valvular lesions			0.103
None	17 (89.5)	16 (76.2)	
Trivial MR	2 (10.5)	2 (9.5)	
Mild MR	0 (0.0)	3 (14.3)	

DISCUSSION

The present study explored the possible risk factors in the presence of right ventricular failure and found that toddy exposure was most common, cited by 17(42.5%) of the patients studied. Other significant associated factors in the study were COPD (14, 35.9%), smoking (12, 30.0%), alcohol consumption (9, 23.7%) and cirrhosis with portal hypertension (5, 12.5%) patients. The results indicate the importance of chronic lung and liver disease, as well as direct effects of habitual toddy consumption on the right ventricle, resulting in failure of the heart's right ventricle. The previous studies have also demonstrated that alcohol-related cardiac injury frequently occurs in association with smoking, pulmonary disease and hepatic dysfunction, which can all contribute to exacerbate the right ventricular load [13][14]. The common features of most patients were NYHA dyspnea grades 2 or 3 (47.5%), exercise limitation (34), bilateral pedal edema (28), fatigue (18), and abdominal distention (13)

patients. This is typical of the usual clinical history of chronic right ventricular failure. Dyspnea, peripheral edema, fatigue and decreased functional capacity have also been previously found to be the most common presenting features of right-sided heart dysfunction [15]. Cardiopulmonary compromise was evident by clinical and laboratory findings. Mean oxygen saturation was low at 83.38 ± 13.32%, PaO2 was 73.28 ± 12.96 mmHg, PaCO2 was 46.00 ± 11.07 mmHg, and FEV1 was reduced to 65.38 ± 22.30. The RVSP was also excessively elevated at 70.68 ± 23.31 mmHg, with LVEF preserved at 60.98 ± 1.21%, confirming predominant right-sided dysfunction, on echocardiogram. Chronic hypoxemia, pulmonary dysfunction and increased pulmonary pressures have also been shown to play a major role in the pathogenesis of right ventricular failure in previous studies [16][17].

The radiologic results confirmed that there was a significant role of underlying lung disease since in many patients emphysema changes, cardiomegaly including pulmonary artery dilatation and fibrotic or interstitial changes were observed while 25.0% patients showed a normal HRCT. Tricuspid regurgitation was mild (37.5%), moderate (27.5%) and severe (32.5%), indicating progressive right heart strain. Past studies have also demonstrated the frequent association of chronic lung disease, pulmonary hypertension and secondary tricuspid regurgitation (TR) in patients with RV failure [18]. The smoking, alcohol, COPD and cirrhosis with portal hypertension were significantly more prevalent in males, whereas the severity of the symptoms and echocardiographic parameters were not markedly different between sexes. This indicated that although there were no differences in the final clinical manifestation of right ventricular failure, men in this group were more burdened with risk factors related to exposures. A greater association of substance-related and pulmonary risk factors is also seen in males in previous studies [19] [20]. In summary, the results indicate that regular consumption of toddy could be a clinically significant yet unrecognised exposure in right ventricular failure. Although causality cannot be inferred from this cross-sectional study, the high prevalence of toddy consumption in conjunction with presence of associated hypoxemia, COPD, portal hypertension, raised RVSP and significant tricuspid regurgitation is a biologically plausible association. Previous studies also corroborate that the cardiovascular damage due to alcohol consumption can be multi-faceted, with hepatic, pulmonary, and myocardial pathways.

CONCLUSION

It is concluded that habitual toddy intake may be an important and underrecognized potential risk factor in patients with right ventricular failure. A considerable proportion of patients in this study had regular toddy exposure, along with coexisting COPD, smoking, hypoxemia, elevated right ventricular systolic pressure, and varying degrees of tricuspid regurgitation. These findings suggest that toddy intake may contribute to right ventricular failure either directly through chronic alcohol-related cardiovascular effects or indirectly through associated pulmonary and hepatic disease.

REFERENCES

1. Al-Yafeai Z, Ali S, Brown J, Venkataraj M, Bhuiyan MS, Faisal ASM, et al. Cardiomyopathy-associated hospital admissions among methamphetamine users. JACC Adv. 2024;3:100840. doi:10.1016/j.jacadv.2024.100840
2. Manja V, Nrusimha A, Gao Y, Sheikh A, McGovern M, Heidenreich PA, et al. Methamphetamine-associated heart failure: a systematic review of observational studies. Heart. 2023;109(3):168–177. doi:10.1136/heartjnl-2022-321610
3. Somma V, Osekowski M, Paratz E, Bonomo Y. Methamphetamine-associated cardiomyopathy: an addiction medicine perspective. Intern Med J. 2023;53(1):21–26. doi:10.1111/imj.15990
4. Breier Y, Azrak E, Banks W, Kushmakov R, Aleshinskaya I. Management of new onset amphetamine-induced acute decompensated heart failure in a young adult: case report. Cureus. 2023. doi:10.7759/cureus.43854
5. Davis JD, Bepo L, Suen LW, McLaughlin MM, Adamo M, Abbs E, et al. Implementing Heart Plus: design and early results of a novel comanagement clinic for patients with stimulant-associated cardiomyopathy. J Card Fail. 2023. doi:10.1016/j.cardfail.2023.10.481
6. Dickson SD, Thomas IC, Bhatia HS, Nishimura M, Mahmud E, Tu XM, et al. Methamphetamine-associated heart failure hospitalizations across the United States: geographic and social disparities. J Am Heart Assoc. 2021;10(16):e018370. doi:10.1161/JAHA.120.018370
7. Richards JR, Harms BN, Kelly A, Turnipseed SD. Methamphetamine use and heart failure: prevalence, risk factors, and predictors. Am J Emerg Med. 2018;36(8):1423–1428. doi:10.1016/j.ajem.2018.01.001
8. Schwarzbach V, Lenk K, Laufs U. Methamphetamine-related cardiovascular diseases. ESC Heart Fail. 2020;7(4):1230–1237. doi:10.1002/ehf2.12572
9. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263–e421. doi:10.1016/j.jacc.2021.12.012
10. Schlezinger JJ, Gokce N. Per/polyfluoroalkyl substances: links to cardiovascular disease risk. Circ Res. 2024;134:1136–1159.
11. Biggeri A, Stoppa G, Facciolo L, Fin G, Mancini S, Manno V, et al. All-cause, cardiovascular disease and cancer mortality in the population of a large Italian area contaminated by perfluoroalkyl and polyfluoroalkyl substances (1980–2018). Environ Health. 2024;23:1–20.
12. Wei Z, Wei K, Yang M, Ying M, Yin Z, Wang N, Zhang L. Kidney function mediates the effects of four per- and polyfluoroalkyl substances on atherosclerotic cardiovascular disease. Ecotoxicol Environ Saf. 2024;288:117395.
13. Chang MC, Chung SM, Kwak SG. Exposure to perfluoroalkyl and polyfluoroalkyl substances and risk of stroke in adults: a meta-analysis. Rev Environ Health. 2024;39:791–800.
14. Dunder L, Salihovic S, Varotsis G, Lind PM, Elmståhl S, Lind L. Plasma levels of per- and polyfluoroalkyl substances and cardiovascular disease—results from two independent population-based cohorts and

a meta-analysis. Environ Int. 2023;181:108250.

15. Wen ZJ, Wei YJ, Zhang YF, Zhang YF. A review of cardiovascular effects and underlying mechanisms of legacy and emerging per- and polyfluoroalkyl substances. Arch Toxicol. 2023;97:1195–1245.
16. Feng X, Long G, Zeng G, Zhang Q, Song B, Wu KH. Association of increased risk of cardiovascular diseases with higher levels of perfluoroalkylated substances in the serum of adults. Environ Sci Pollut Res Int. 2022;29:89081–89092.
17. Schillemans T, Donat-Vargas C, Lindh CH, de Faire U, Wolk A, Leander K, Åkesson A. Per- and polyfluoroalkyl substances and risk of myocardial infarction and stroke: a nested case-control study in Sweden. Environ Health Perspect. 2022;130:037007.
18. Wittkopp S, Wu F, Windheim J, Robinson M, Kannan K, Katz SD, Chen Y, Newman JD. Vascular endothelium as a target for perfluoroalkyl substances. Environ Res. 2022;212:113339.
19. Meneguzzi A, Fava C, Castelli M, Minuz P. Exposure to perfluoroalkyl chemicals and cardiovascular disease: experimental and epidemiological evidence. Front Endocrinol (Lausanne). 2021;12:706352.
20. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, Tousoulis D. Inflammatory mechanisms contributing to endothelial dysfunction. Biomedicines. 2021;9:781.