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Clinical characteristics, evaluation and outcomes of chylopericardium: a systematic review

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ABSTRACT

Objective Chylopericardium (CPE) is a rare condition associated with accumulation of triglyceride-rich chylous fluid in the pericardial cavity. Due to minimal information on CPE within the literature, we conducted a systematic review of all published CPE cases to understand its clinical characteristics, management and outcomes.

Methods We performed a literature search and identified cases of patients with CPE from 1946 until May 2021 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We identified relevant articles for pooled analyses of clinical, diagnostic and outcome data.

Results A total of 95 articles with 98 patients were identified. Patient demographics demonstrated male predominance (55%), with a mean age of 37±15 years. Time from symptom onset to diagnosis was 5 (Q1 4.5, Q3 14) days, with 74% of patients symptomatic on presentation. Idiopathic CPE (60%) was the most common aetiology. Cardiac tamponade secondary to CPE was seen in 38% of cases. Pericardial fluid analysis was required in 94% of cases. Lymphangiography identified the leakage site in 59% of patients. Medical therapy (total parenteral nutrition, medium-chain triglycerides or octreotide) was undertaken in 63% of cases. In our cohort, 32% progressed towards surgical intervention. During a median follow-up of 180 (Q1 180, Q3 377) days, CPE recurred in 16% of cases. Of the patients with recurrence, 10% were rehospitalised.

Conclusion CPE tends to develop in younger patients and may cause serious complications. Many patients fail medical therapy, thereby requiring surgical intervention. Although overall mortality is low, associated morbidities warrant close follow-up and possible reintervention and hospitalisations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chylopericardium (CPE) is a rare condition resulting from chylous fluid accumulation in the pericardial sac.

⇒ Minimal research exists on understanding its associated clinical characteristics.

WHAT THIS STUDY ADDS

⇒ The results of our study suggest that patients who develop CPE tend to be younger and that a substantial number of patients fail medical management and thereby require surgical intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Close monitoring is important as there is significant associated morbidity in CPE.

INTRODUCTION

Chylopericardium (CPE) or chylous pericardial effusion is a rare disease associated with accumulation of triglyceride-rich fluid in the pericardial space. The aetiology of CPE is multifactorial.[1] The primary causes are idiopathic/viral, whereas the secondary causes include postcardiothoracic surgery, radiation exposure, trauma, malignancy and infection.[2] The proposed mechanism of CPE is attributed to lymphatic system damage, leading to abnormal communication between the thoracic duct and the pericardial lymphatic channels. This results in the outflow of chyle into the pericardial space from the lymphatic duct and subsequent accumulation. There is a paucity of literature describing the epidemiology, natural history and outcomes in CPE, and to our knowledge only one prior systematic review on CPE exists.[3] Therefore, we aimed to conduct a systematic review to study the clinical characteristics and outcomes of patients with CPE, specifically investigating their clinical course and the role of multimodality imaging in diagnosis and management.

METHODS

A comprehensive search was performed on 2 December 2020 for published articles on chylous pericardial effusion in the following databases: Ovid Medline, Ovid Embase, CINAHL from EBSCOhost, Scopus (Elsevier), Web of Science's BIOSIS Citation Index, Science Citation Index Expanded and Conference Proceedings Citation Index-Science. The search was updated on 27 May 2021.

Indexing terms and keywords for both chyle and pericardial effusion or chylopericardium were combined without any language filters. All publication types were considered, and all databases were searched for the concepts. We reviewed identified articles for our selection strategy. Although our inclusion criteria included case reports, we also searched for potential observational studies, clinical trials and registry reports seeking information on CPE. Letters to the editors, animal/paediatric

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studies and publications in languages other than English were excluded.

We designed our systematic review based on the PICO (patient, intervention, control and outcome) framework. Adult patients (≥18 years) with CPE constituted our study population, medical±surgical therapy composed our intervention, and mortality during index hospitalisation, recurrence of CPE, reinterventions (pericardiocentesis, pericardial window or pericardiectomy), rehospitalisation and mortality after discharge were considered as outcomes. Due to paucity of observational studies, we did not include any comparison group for our analysis. Patient and public involvement is not applicable in this study.

Two independent researchers (AK and AA) screened articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[4] Another reviewer (BV) assisted in the resolution of any conflict during the selection process. Our study used the online tool Covidence to collect, screen and store the selected articles. Indepth information was manually collected from online text manuscripts, tables and figures of the selected articles. Abstracts, review articles, letter to the editors, publications in language other than English, animal studies and studies exclusive to paediatric populations were excluded.

Qualitative data analysis approach involved content analysis to report patterns and frequencies. Extracted data were compiled/pooled for statistical analysis and reporting of the results. Results were presented as clinical characteristics, diagnostic approach, management strategy and outcomes. Categorical variables were represented as proportions (%) and continuous variables as mean (SD). Due to lack of study-level data on this topic, the techniques of meta-analysis for meta-proportion or meta-binary calculations of effect sizes and test of heterogeneity were not feasible.

RESULTS

Our search identified 1169 articles. After deduplication (n=613), 556 articles were screened by title and abstract. Of the articles, 289 met the criteria for full-text screening, of which 95 case reports (98 patients) comprised our final study cohort (figure 1, online supplemental table 1). No observational studies, randomised control studies or clinical trials were identified.

Pooled individual patient-level data demonstrated that our cohort (n=98) had a mean age of 37±15 years and that most patients were male (55%, n=53). CPE was reported as the first occurrence in 97% (n=95) of cases and the median time to symptom onset from diagnosis was 5 (Q1 4.5, Q3 14) days. Majority of the CPE cases were reported in the USA (30%, n=29), followed by the Middle East (16%, n=16) and Europe (16%, n=16). Patient comorbidities included malignancy (12%, n=12), valvular surgery (11%, n=11) and coronary artery bypass grafting (7%, n=7). The predominant aetiology was idiopathic/viral (60%, n=60), followed by postcardiac injury syndrome (23%, n=23) and malignancy (11%, n=11). Dyspnoea (38%, n=39) was the most common initial presenting symptom. Concomitant pericarditis occurred in 7% (n=7) of cases. Cardiac tamponade was seen in 38% (n=37) of cases (table 1).

Pericardial fluid analysis confirmed CPE in 94% (n=92) of cases. The median cholesterol and triglyceride levels were 105 mg/dL (Q1 55, Q3 136) and 874 mg/dL (Q1 552, Q3 1351), respectively. The median serum erythrocyte sedimentation rate (ESR) was 14 mm/hour (Q1 5, Q3 22). Chest X-ray (CXR) most frequently revealed cardiomegaly (88%, n=52). Fifty-one patients underwent transthoracic echocardiogram, revealing pericardial effusion as small (6%, n=3), moderate (14%, n=7) or large (80%, n=41). The predominant CT chest finding was pericardial effusion (45%, n=15). Cardiac magnetic resonance (CMR) imaging was performed in 10% of cases, and pericardial effusion (70%, n=7) and pleural effusion (20%, n=2) were the most common findings identified. Lymphangiography was required in 59% (n=49) of cases and was able to identify the thoracic duct as the predominant leakage site (70%, n=14) (table 2).

Conservative medical management (63%, n=62) included total parenteral nutrition (TPN), medium-chain triglyceride diet (MCTD) or octreotide for a median of 10 (Q1 6, Q3 15) days. Concomitant medical and surgical intervention was undertaken in 16% (n=16) of cases. Progression to surgical management secondary to failure of medical management was reported in 34% (n=33) of cases. Thoracotomy or video-assisted thoracoscopic surgery was required in 35% (n=34) of cases, thoracic duct ligation in 32% (n=31) and pericardiectomy in 15% (n=15) (table 3).

Follow-up was reported in 72% of cases, with a mean follow-up time of 180 (Q1 90, Q3 377) days. Six (6%) patients died secondary to underlying comorbidities. Rehospitalisation for recurrent dyspnoea or reaccumulation of effusion occurred in 10% (n=10) of our cohort. CPE recurred in 16% (n=16)

Table 1 Clinical characteristics of our study cohort (n=98)

Demographics	
Age (years)	37 (±15)
Male	53 (55)
Country	
USA	29 (30)
Middle East	16 (16)
Europe	16 (16)
Japan	12 (12)
Other	25 (26)
Presentation	
First	95 (97)
Recurrent	3 (3)
Symptomatic	73 (74)
Asymptomatic	26 (26)
Dyspnoea	38 (39)
Chest discomfort/pain	11 (11)
Abdominal discomfort/pain	5 (5)
Enlarged cardiac silhouette	6 (6)
Other	15 (15)
Shock	4 (4)
Cardiac tamponade	37 (38)
Aetiology	
Idiopathic/viral	60 (61)
Postcardiac injury syndrome	23 (23)
Malignancy	11 (11)
Other	4 (4)
Time to symptoms onset (days)	4.8 (4.5–14)
Concomitant pericarditis	7 (7)
Medical history	
Coronary artery bypass graft	7 (7)
Valve surgery	11 (11)
Malignancy	12 (12)

Values are presented as mean (±SD), absolute numbers with associated percentages or as median with IQR.

Table 2 Diagnostic findings of chylopericardium

Fluid analysis (n=98)	
Diagnosis confirmed via fluid analysis	92 (94)
Cholesterol (mg/dL)	105 (55–136)
Triglycerides (mg/dL)	874 (552–1351)
Erythrocyte sedimentation rate (mm/hour)	14 (5–22)
Chest X-ray (n=59)	
Enlarged cardiac silhouette	52 (88)
Pleural effusion	5 (8)
Pneumopericardium	2 (3)
Pericardial effusion on echocardiography (n=51)	
Small	3 (6)
Moderate	7 (14)
Large	41 (80)
CT (n=33)	
Pericardial effusion	15 (45)
Cardiac MRI (n=10)	
Pericardial effusion	7 (70)
Pericardial enhancement	1 (10)
Pleural effusion	2 (20)
Other	3 (30)
Lymphangiography (n=49)	
Accumulation of fluid in the pericardial sac	30 (55)
Accumulation of fluid in the mediastinum	5 (9)
Thoracic duct fluid accumulation	14 (70)

Values are presented as absolute numbers with associated percentages or as median with IQR.
VATS, video assisted thoracoscopic surgery.

of cases, while 6% (n=6) required repeat pericardiocentesis or pericardial window (table 4).

DISCUSSION

This systematic review examines and analyses the clinical characteristics and associated mortality and morbidity of patients with CPE. There is limited literature on CPE, and to our knowledge no discrete observational studies exist.

The European Society of Cardiology (ESC) 2015 guidelines suggest CPE can have a variable presentation that ranges from asymptomatic to emergent cardiac tamponade.[1] Cardiac complications can include development of acute and constrictive pericarditis.[1] Furthermore, it should be noted that CPE rarely presents with concomitant pericarditis (7%). Therefore, this suggests that CPE is primarily a rare aetiological cause of pericardial effusion as compared with a rare cause of acute pericarditis. CPE's primary aetiology is idiopathic, and CPE most commonly presents with dyspnoea.[3] Epidemiological estimates of the prevalence of CPE are currently unknown. Our results demonstrated

Table 3 Management of chylopericardium (n=98)

Conservative/medical management	62 (63)
Duration of medical/conservative therapy (days)	10 (6–15)
Failure of medical/conservative therapy	33 (34)
Thoracotomy or VATS	34 (35)
Thoracic duct ligation	31 (32)
Combined surgery and ligation	16 (16)
Pericardiectomy	15 (15)

Values are presented as absolute numbers with associated percentages or as median with IQR.
VATS, video-assisted thoracoscopic surgery.

Table 4 Outcomes in patients with chylopericardium (n=98)

Death (at follow-up)	6 (6)
Rehospitalisation	10 (10)
Recurrent chylopericardium	16 (16)
Repeat pericardiocentesis	6 (6)
Repeat pericardial window	3 (3)
Development of pericarditis	2 (2)
Development of constrictive pericarditis	1 (1)
Development of cardiac tamponade	1 (1)
Regular follow-up	71 (72)
Follow-up (days)	180 (90–377)

Values are presented as bsolute numbers with associated percentages or as median with IQR.

that CPE has a higher prevalence in developed countries. This may be due to the higher number of patients receiving cardiac surgery and radiation therapy.[3 5 6]

The proposed pathophysiology of CPE development is damage to the thoracic duct, leading to abnormal communication of lymphatic vessels between the thoracic duct and the pericardial space. This results in heightened thoracic duct pressure, yielding outflow of chyle into the pericardial space from the thoracic duct.[7]

Imaging findings of CPE are often variable and non-specific for confirmatory diagnosis. CXR, echocardiography (echo), CT, CMR imaging and lymphangiography are the various modalities needed for diagnosis and management.[3] CXR will often show enlarged cardiac silhouette, and identification on imaging should direct further evaluation for CPE. Echo is instrumental in detecting the presence of pericardial effusion secondary to CPE. Furthermore, echo can quantify effusion size and haemodynamic impact. However, notably echo does not provide information about the underlying pericardial effusion cause.[8]

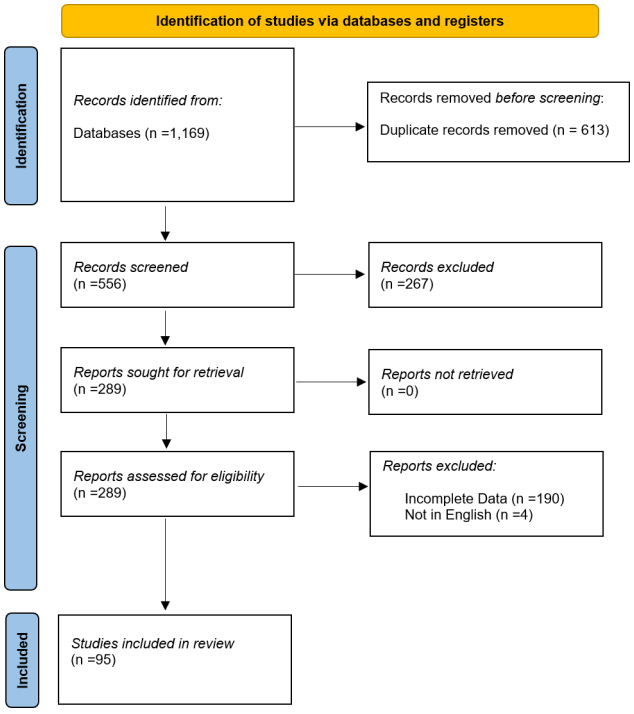

Figure 1 PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

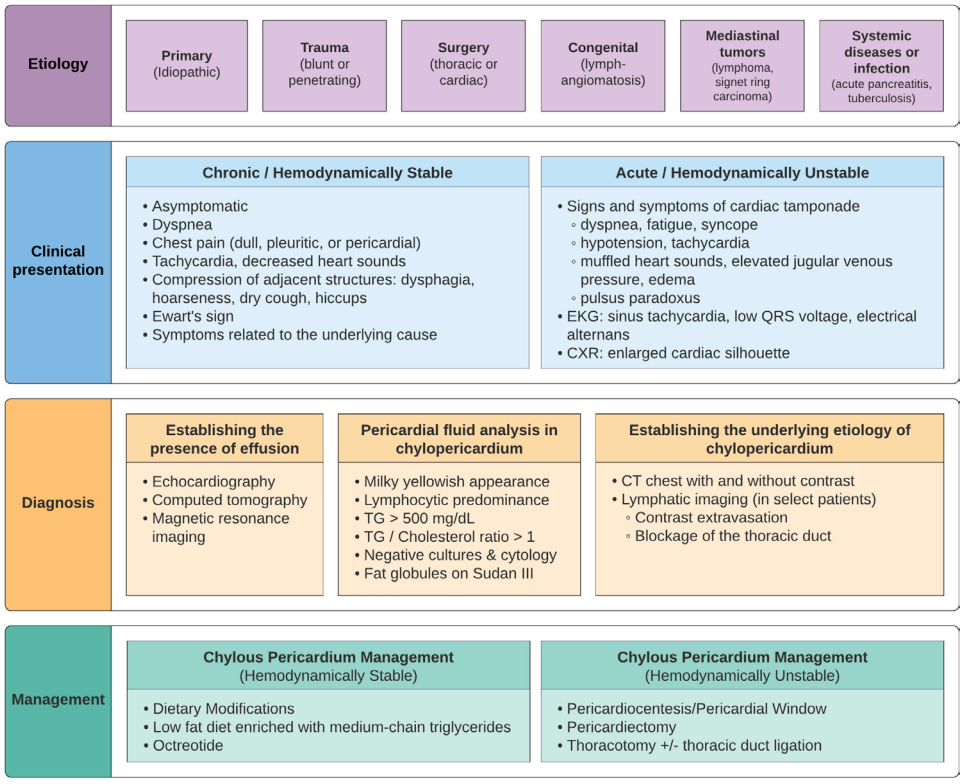

Figure 2 Breakdown of causes of chylopericardium with associated clinical presentation, diagnosis and management strategies. CXR, chest X-ray; TG, triglyceride.

In the setting of pericardial disease, echo is also the initial diagnostic modality for patients who develop or are clinically suspected to have cardiac tamponade or constrictive pericarditis (figure 2). Findings of collapse of the right atrium during systole, presence of inferior vena cava plethora and large pericardial effusion on echo may suggest concomitant cardiac tamponade. Septal bounce, respiratory variation of the mitral and tricuspid inflows on Doppler, plethoric inferior vena cava, and hepatic vein flow diastolic reversal during expiration are suggestive of constrictive pericarditis on echo.[9] CT can also provide information about the localisation and quantification of pericardial effusion especially in cases of anterior and superior loculated effusions, which are difficult to detect on echocardiogram.[9] CMR is not routinely performed for diagnosis and management of CPE, attributed to its accessibility and high cost in the real-world setting. However, in the setting of pericardial disease, CMR is particularly helpful in pericardial tissue characterisation, specifically identification of inflammation and oedema and assessment of pericardial thickness.[9] Suggestive features of constrictive pericarditis on CMR include septal bounce, sudden termination of diastolic filling or respirophasic discrepancy in septal excursion.[9] Lymphangiography is used most frequently for anatomical assessment of lymphatic leakage and can greatly guide surgical management of CPE.[10]

Confirmatory diagnosis of CPE requires pericardial fluid analysis either via pericardiocentesis or pericardial window. High triglyceride concentration >500 mg/dL, cholesterol to triglyceride ratio less than 1, Sudan III staining, negative fluid cultures and lymphocyte predominance support the diagnosis.[3] Although current guidelines suggest that ESR and C reactive protein levels should be elevated, in addition to the standard criteria for confirmatory diagnosis of pericarditis, we found that the median ESR was 14 mm/hour, suggesting no active inflammatory state.[1 11 12]

Initial treatment of CPE is dependent on the presenting haemodynamic status. A multidisciplinary team of cardiologists, cardiothoracic surgeons and interventional radiologists is required. When haemodynamically stable, in accordance with the 2015 ESC guidelines, initial conservative treatment with TPN, MCTD and octreotide is instituted.[1 13 14] TPN and MCTD diminish lymph flow and intralymphatic pressure, while octreotide reduces thoracic duct flow rate and chyle production.[3 13] Octreotide has been shown specifically to be therapeutic in patients with CPE secondary to surgery and malignancy.[15] Per 2015 ESC guidelines, in patients who are symptomatic or present with cardiac tamponade, pericardiocentesis may be needed.[1] Unfortunately, some patients experience failure of medical management, thereby requiring surgical intervention. In most cases, surgery with thoracic duct ligation is curative.[16–18] Pericardiectomy may also be considered in recalcitrant patients or in those who develop constrictive physiology.[19]

We found that mortality among CPE cases is low and is attributed to underlying comorbidities such as malignancy. These patients are also at risk of recurrent CPE, which may require further interventions, such as pericardiocentesis, pericardial window or rehospitalisation.

From a clinical standpoint, our study reiterates the need for close follow-up and surveillance in patients with CPE due to its association with cardiac tamponade, recurrent nature and associated morbidity.

Study limitations

Our study has some expected limitations. Overall, there were less than 100 included patients, thereby restricting the power neccessary to perform multivariable analyses. However, this is the largest systematic review of patients with CPE in the literature. Information was pooled together from the case reports,

therefore limiting their generalisability. Case reports from the individual centres could vary in quality and amount of data presented. Under-reporting could underestimate our outcomes providing lower estimates. Due to the inherent nature of the study design, we were unable to compare our cases with a control group, hence limiting validation of treatment effect.

CONCLUSION

CPE is a rare clinical condition with presentations ranging from asymptomatic to emergent cardiac tamponade. Literature on this topic largely comprises case reports. CPE management is complex and requires a multidisciplinary team. A subset of patients may fail medical therapy, thereby necessitating surgical intervention. While CPE mortality is low, morbidity associated with the disease is high. Therefore, sufficient consideration should be taken during diagnosis and management of patients.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplemental Appendix

Supplemental Table 1: Chylopericardium cases with notable characteristics

Supplemental References

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Supplemental Table 1: Chylopericardium cases with notable characteristics

Author	Year	Age	Gender	Symptomatic	Tamponade	Recurrent CPE	Death
Chaloob et al[1]	2008	50	M	1	1	0	0
Wang et al[2]	2000	61	M	1	0	0	0
Mundra et al[3]	2011	54	M	1	1	0	0
Lee et al[4]	2017	26	F	1	1	0	0
Rafiq et al[5]	2016	32	F	1	1	0	0
Sasaki et al[6]	2002	49	M	0	0	0	0
Raza et al[7]	2009	39	F	1	1	1	0
Raya et al[8]	2017	28	F	1	1	0	0
Sakata et al[9]	2000	20	M	0	0	0	0
Raza et al[7]	2009	33	F	1	1	1	0
Mistui et al[10]	2005	27	F	1	0	0	0
Cheng et al[11]	2013	59	M	1	1	0	0
Cheng et al[11]	2013	45	F	1	0	0	0
O'Donnell et al[12]	2019	39	M	1	1	1	0
Knight et al[13]	1965	62	M	1	1	0	0
Malhotra et al[14]	2018	21	F	1	1	0	0
Bar-El et al[15]	1989	39	F	1	1	1	0
Mood et al[16]	2006	34	M	0	1	0	0
Adekile et al[17]	2009	34	M	1	1	0	0
Morishita et al[18]	1985	25	M	0	0	0	0
de Winter et al[19]	1994	40	F	0	0	1	0

Yildirim et al[20]	2009	24	F	1	0	0	0
Kannagi et al[21]	1982	23	M	1	0	0	0
Morris et al[22]	2019	68	F	1	0	1	0
Lee et al[23]	1987	49	M	1	1	0	0
Kamata et al[24]	2017	54	M	1	1	0	0
Kalimuthu et al[25]	2020	47	M	0	0	1	0
Barton et al[26]	1980	48	M	1	0	0	0
Rankin et al[27]	1980	19	F	0	0	0	0
Barbetakis et al[28]	2010	41	F	1	1	0	0
Chavez et al[29]	1973	27	M	0	0	0	0
Karaca et al[30]	2014	47	M	1	0	0	0
Charnilas et al[31]	1977	18	F	0	0	0	0
Wilmshurst et al[32]	1986	21	F	0	0	1	0
Weyne et al[33]	1987	25	M	1	0	0	0
Luo et al[34]	2018	33	F	0	0	0	0
Nanjo et al[35]	2004	47	M	1	0	0	0
Nanjo et al[35]	2004	21	F	1	0	1	0
Niznansky et al[36]	2015	48	F	1	1	0	0

Yokusoglu et al[37]	2005	36	M	0	0	0	0
Gallant et al[38]	1977	19	F	0	0	0	0
Holder et al[39]	2020	26	F	1	0	0	0
Sehgal et al[40]	2017	46	F	1	1	0	1
Svedjeholm et al[41]	1997	51	F	1	0	0	0
Swelstad et al[42]	2003	31	F	1	1	0	0
Szabados et al[43]	2011	46	F	1	0	0	0
Yu et al[44]	2018	57	M	1	0	1	0
Van Elden et al[45]	2014	42	M	1	0	0	0
Coplu et al[46]	1992	25	M	1	0	0	0
Goldstein et al[47]	1969	21	F	0	0	1	0
Silva et al[48]	2009	20	F	1	0	1	0
Tuncay et al[49]	2016	22	F	1	0	0	0
Obeidat et al[50]	2020	28	F	1	1	0	0
Chia et al[51]	2020	67	M	1	1	0	0
Hattori et al[52]	2011	30	F	1	0	0	0
Feldman et al[53]	2001	40	M	1	1	0	0
Ozturk et al[54]	2017	56	F	1	1	1	1
Mogulkoc et al[55]	1999	19	F	1	0	0	1

Miyoshi et al[56]	2008	58	F	1	0	0	0
Ross et al[57]	1979	19	M	0	0	0	0
Fawal et al[58]	1967	36	M	1	0	0	0
Arendt et al[59]	1996	47	F	1	0	0	0
Yang et al[60]	2017	52	M	0	0	0	0
Koutsogiannidis et al[61]	2013	36	F	0	0	0	0
Lippman et al[62]	2016	50	M	1	1	0	0
Lara et al[63]	2019	42	M	1	0	0	0
Lee et al[64]	2006	25	M	1	1	0	1
Bewick et al[65]	1984	42	F	1	0	0	0
Girard et al[66]	2019	33	F	1	1	0	0
Bhat et al[67]	2011	19	M	1	1	0	0
Chew et al[68]	2014	66	M	1	0	1	0
Borulu et al[69]	2020	62	M	1	0	0	0
Akamatsu et al[70]	1994	24	M	0	0	0	0
Revere et al[71]	2007	18	F	1	1	0	0
Mehrotra et al[72]	2006	22	M	1	1	0	0
Mandarry et al[73]	2012	19	M	1	1	0	0
Stewart et al[74]	2009	45	M	0	1	0	0
Rosa et al[75]	2014	58		1	1	0	0

Selimoglu et al[76]	2008	67	M	1	0	0	0
Gilmore et al[77]	2012	48	F	1	0	0	0
Kashyap et al[78]	2011	21	F	1	0	0	0
Sanso et al[79]	2016	31	M	1	1	0	1
Gupta et al[80]	2017	49	F	1	1	0	0
de Santis et al[81]	2020	56	M	1	0	0	0
Mi et al[82]	2020	51	M	1	0	0	0
Liberman et al[83]	2006	45	M	1	0	0	0
Katabi et al[84]	2020	24	M	0	1	0	0
Savran et al[85]	1975	29	M	0	0	0	0
Vinaykumar et al[86]	2014	18	M	0	0	0	0
Melduni et al[87]	2008	74	M	1	0	0	0
Matsuyama et al[88]	2003	20	M	0	0	0	0
Jenner et al[89]	1975	30	F	1	0	0	0
Kawthar et al[90]	2020	33	F	0	0	0	0
Mahon et al[91]	2003	25	M	0	0	1	0
Koksel et al[92]	2007	25	M	1	0	0	0
Barillas et al[93]	2021	26	M	1	0	0	1
Reddy et al[94] x[95]	2021	27	F	1	0	0	0

CPE: Chylopericardium

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