

**Trends in the utilization of outcome measures for protein-losing enteropathy in contemporary Fontan studies: a systematic review**

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**Objectives.** Appropriate selection and standardization of outcome measures are important for advancing Fontan care and research. No study has assessed the use of outcome measures in Fontan studies on protein-losing enteropathy (PLE). The present study determined whether outcome measures of PLE are routinely reported, and to identify the types of outcome measures used in order to classify them in subsets of clinically meaningful endpoints.

**Methods.** A systematic review was conducted in adherence to the PRISMA recommendations. A PubMed search was done on papers published between January 2007 – December 2016 (10 years) using the keywords Fontan AND protein-losing enteropathy. All studies reporting outcome of Fontan patients with PLE were included. We defined an outcome measure as any measurable variable used to describe clinical outcome or effect of a medical intervention. Only variables specific for PLE outcome were selected. Where patient outcome was descriptive (case reports and case series), information was retracted from the text and quantitatively analysed using a lateral thinking tool in which outcome measures were fractionated into objective and constituent pieces of information. Outcome measures were then categorized into appropriate outcome domains.

**Results.** We identified 162 papers. In the final analysis, data from 77 published articles were extracted, including the outcome of 716 Fontan patients with PLE. A total number of 414 outcome measures were reported, including 115 surrogate outcome measures (27.8%). The number of unique outcome measures ranged from 1 to 17 per study. The five most common outcome domains were PLE relapse/resolution (57 [74.0%] studies), survival (51 [66.2%]), PLE symptoms (30 [38.9%]), edema (21 [27.3%]), and ascites (21 [27.3%]). Importantly, most studies did not define PLE relapse or resolution. A biochemical assessment of disease activity (serum albumin or protein level) was documented in 40 (51.9%) reports, whereas enteric protein loss was quantified in only 12 (15.6%) studies.

**Conclusions.** The outcomes reported in contemporary Fontan-PLE studies are extremely heterogeneous. Thus, there is a great need to develop validated outcome measures to objectively assess disease severity and to quantify the true effectiveness of any therapeutic intervention in Fontan patients with PLE.