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Mini Review

Is Albumin Dialysis a Viable Option in Acute Liver Failure and Other Liver Pathologies?

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Abstract

Acute liver failure (ALF) is associated with a significant 3-month mortality rate of up to 47%. Effective management of ALF requires accurate identification of the underlying cause, careful assessment of encephalopathy severity, and proficient management of potential complications. Liver transplantation is the recommended treatment option for patients with a low probability of spontaneous recovery. This approach has demonstrated consistently positive outcomes reported in both short- and long-term studies. However, for patients with liver failure awaiting transplantation or recovery, albumin dialysis (an extracorporeal nonbiologic liver support system most extensively researched) is considered the most effective option for bridge or destination therapy. Molecular adsorbent recirculating system (MARS) and fractionated plasma separation and absorption device (Prometheus) are two albumin dialysis systems that have been clinically applied to a variety of liver pathologies. This paper provides a narrative review of the various applications of these devices, with a particular focus on their efficacy in the management of ALF and acute-on-chronic liver failure.

Keywords: *Albumin Dialysis; MARS; Promethus; Acute Liver Failure; Acute on Chronic Liver Failure*

Abbreviations

ALF: Acute Liver Failure; LT: Liver transplantation; ELS: Extracorporeal Liver Support; MARS: Molecular Adsorbent Recirculating System; Prometheus: Fractionated Plasma Separation and Absorption Device; ACLF: Acute on Chronic Liver Failure; RCTs: Randomized Control Trials; HILI: Hypoxic Liver Injury; PHLF: Post-Hepatectomy Liver Failure; DILI: Drug-Induced Liver Injury; VAS: Visual Analogue Scale; MELD: Model for End-Stage Liver Disease; SMT: Standard Medical Therapy

Introduction

Acute liver failure (ALF) constitutes 7% of all liver transplantation (LT) indications in the United States [1]. Globally, viral hepatitis is considered the leading cause of ALF, while drug-induced liver injury, particularly from acetaminophen, accounts for approximately 50%

of cases in developed countries [2,3]. In severe cases of ALF, LT is the only curative option. Before LT became available, the mortality rate of ALF ranged between 80% and 85% [4]. The waiting list for LT is ever expanding and nearly 25% of patients die while waiting for transplant [5]. Considering this, extracorporeal liver support (ELS) techniques are being explored to serve as a bridge to LT in AFL, providing stability while on the waiting list.

ELS is divided into two categories: artificial and biological. Artificial ELS mainly involves albumin dialysis and high-volume plasma exchange. In albumin dialysis, toxins in the blood are filtered using the capacity of albumin to bind with them. While there are many systems that utilize albumin dialysis, two have been extensively implemented and studied in a clinical setting [6]. These are the molecular adsorbent recirculating system (MARS) and fractionated plasma separation and absorption device (Prometheus). MARS uses two separate dialysis circuits to eliminate protein-bound and water-soluble toxins [7]. To remove albumin-bound toxins, the system employs activated charcoal and an anion exchanger. In contrast, Prometheus employs fractionated plasma separation, adsorption, and hemodialysis [8]. It uses a semipermeable membrane to generate a plasma-like solution containing albumin. The patient's plasma solution then passes through albumin-detoxifying columns before being reunited with blood cells. Finally, hemodialysis is performed to remove water-soluble solutes. This technique uses the patient's own albumin, eliminating the need for exogenous albumin.

Studies have demonstrated promising results in utilizing these devices, opening new avenues for the treatment of various liver pathologies. This review aims to assess the current clinical applications of MARS and Prometheus in the management of ALF, acute-on-chronic liver failure (ACLF) and other liver conditions.

MARS

Since its inception in 1998, MARS has been extensively utilized and studied [9]. This technique has been used in ALF, acute on chronic liver failure, end-stage liver disease as a bridge to transplantation, hepatorenal syndrome, refractory pruritus, hepatic encephalopathy, drug intoxication, and post-transplant liver failure.

Acute liver failure

The MARS device has demonstrated efficacy in eliminating water-soluble and lipophilic substances from the bloodstream, leading to a reduction in hepatic encephalopathy and systemic circulatory shock in patients with ALF [10-13]. However, there is paucity of data on the impact of MARS therapy on patient survival in ALF due to the limited number of randomized controlled trials (RCTs) [10]. One RCT did not show a significant survival advantage with MARS therapy when compared to standard medical therapy in ALF patients. However, the inclusion criteria of the RCT may have influenced the outcomes, as almost two-thirds of the patients had already undergone transplantation before receiving MARS treatment [10]. Notably, subgroup analyses revealed that patients who underwent at least three MARS sessions experienced improved survival, suggesting that MARS therapy may benefit individuals who are not eligible for emergency liver transplantation. Additionally, early initiation of MARS therapy may be crucial for optimal efficacy [10,14]. The findings of a multicenter study suggest that MARS therapy is associated with significantly enhanced 21-day survival without requiring a transplant in patients diagnosed with ALF [15].

Acute on chronic liver failure

The use of MARS has been shown to effectively eliminate a range of substances that accumulate in patients with ACLF, such as bilirubin, ammonia, cytokines, and free fatty acids [16]. Numerous RCTs have investigated the effects of albumin dialysis in ACLF patients [17-23]. One study demonstrated that patients treated with MARS had significantly lower levels of serum bilirubin and creatinine, as well as better 7-day survival rates when compared to patients treated with hemodiafiltration [23]. Another RCT revealed that MARS therapy significantly decreased serum bilirubin levels and mortality rates [17]. A third controlled trial indicated that albumin dialysis improved the rate of recovery from hepatic encephalopathy in comparison to standard medical therapy [24]. However, the RELIEF study, which included

189 ACLF patients, did not show a beneficial effect on survival [18]. For the most part, conventional meta-analyses have yielded mixed results, with some studies indicating no effect of artificial liver support systems on mortality.

Other liver pathologies

MARS has demonstrated efficacy in relieving cholestatic pruritus over an extended period. In one study, MARS therapy led to a significant reduction in itch measured by a visual analogue scale (VAS) [25]. The VAS score demonstrated a reduction of 72% immediately following treatment and by 51% after one month [25]. Other studies have also noted significant improvements in pruritus and quality of life after MARS therapy [25,26]. In the evaluation of 15 patients referred for liver transplantation suffering from intractable pruritus, the safety and efficacy of MARS treatment were investigated. The treatment resulted in an immediate and complete response in 11 patients, and no significant adverse events were reported [26].

Hypoxic liver injury (HILI) is a frequent occurrence in critically ill patients and is characterized by a marked elevation in aminotransferase levels. Several studies have shown that MARS can potentially enhance survival rates and decrease the requirement for vasopressor support, leading to better outcomes [27,28]. However, further studies involving larger cohorts are necessary to validate these results and to compare the efficacy of MARS to other dialysis devices.

Post-hepatectomy liver failure (PHLF) is a severe complication caused by small-for-size situations or early post-operative complications. A retrospective review of two institutions and a prospective pilot trial indicated promising outcomes in PHLF patients who received early and frequent treatment with MARS [29]. Nonetheless, the current evidence is insufficient to answer critical questions regarding the initiation of treatment, optimal number and duration of sessions, and patient selection. Further studies are necessary to address these gaps in knowledge.

Drug-induced liver injury (DILI) can manifest as cholestatic, hepatocellular, or a combination of both patterns. Specifically, in cholestatic injury, MARS has been effective, as reported by case reports [30-32]. Some of hepatotoxic medications included: phentermine, methimazole, and methyl-1-etiocholenololepietiocholanolone and OxyElite [31]. In all these cases, there was a significant reduction in bilirubin and complete resolution of the liver injury [31].

Safety profile

MARS is generally considered a safe treatment option, but there are potential complications to consider. While air embolism is rare, it poses similar risks to other central venous accesses used for non-albumin dialysis purposes [10]. Thrombocytopenia and decreased fibrinogen levels are frequent and expected to decrease by 15 - 20% after treatment [10]. It is advised to avoid starting MARS treatment when the platelet count is below 50,000/μL and fibrinogen is below 1 g/L. Although bleeding and thrombosis are rare, close monitoring is necessary. Bleeding typically manifests as oozing from the venous access site, while venous access thrombosis occurs in 1 - 2% of cases [10]. Despite slight decreases in hemoglobin and leukocytes or increases in prothrombin time, no clinically significant events have been reported.

Prometheus

Prometheus was first introduced in 1999. Since its inception, the technique has been compared to the MARS and shown to potentially perform better than MARS in filtering bilirubin and ammonia [33]. The placement of the high flux dialyzer within the albumin circuit of a patient's bloodstream when using Prometheus increases the risk of thrombosis. As a result, anticoagulation is often necessary to mitigate this risk, which is a drawback of using this method [34].

Acute liver failure

Prometheus has consistently demonstrated significant reductions in multiple compounds such as bilirubin, ammonia, aspartate aminotransferase, urea, and creatinine in ALF [35,36]. Rifai., *et al*. measured the filtration of specific amino acids through Prometheus and at-

tributed this to the reduction in the development of hepatic encephalopathy [36]. These amino acids include glutamine, tyrosine, phenylalanine, and tryptophan [36]. Another mechanism contributing to the reduction of hepatic encephalopathy risk in patients treated with Prometheus can be attributed to the alteration of intracranial pressure [34]. A study by Oppert., *et al*. specifically comparing the survival rate in patients with ALF vs. ACLF with the use of Prometheus demonstrated better survival rates for ALF patients [37]. No comparison was made with medical treatment to determine any mortality benefit. Importantly, another study exclusively conducted on a population of ALF patients after major cardiac and vessel surgery showed a significant decline in bilirubin levels and an overall positive effect on liver synthetic function with a 23% survival rate [38].

Acute on chronic liver failure

There have been limited studies conducted in ACLF patients. The first study conducted demonstrated a significant decrease in the lab parameters but no improvement regarding development of hepatic encephalopathy [36]. In a small study (n = 9) of patients with ACLF, Evenpoel., *et al*. found that the Prometheus device was well-tolerated and had significant efficacy in removal of albumin binding toxins [39]. In contrast, the HELIOS study did not find a significant difference in the overall survival with Prometheus therapy [40]. However, a subgroup analysis revealed that patients with type 1 hepatorenal syndrome (HRS) or a Model for End-Stage Liver Disease (MELD) score > 30 had a statistically significant survival advantage with Prometheus treatment. More precisely, the Prometheus group had higher survival probabilities at 28 and 90 days compared to the medical therapy-alone [40].

Other liver pathologies

Unlike MARS, Prometheus has primarily been used for ALF and ACLF and has not been extensively studied for other indications. A single study investigated the use of Prometheus for cholestatic pruritus, demonstrated a significant reduction in VAS and improved pruritus over four weeks [41].

Safety profile

Prometheus treatments can cause a transient increase in white blood cell count [42]. Although there has been one reported case of significant thrombocytopenia, no bleeding complications have been associated with Prometheus to date. During treatment, there may be a decrease in albumin levels that reinfusion of the extracorporeal plasma volume may not fully compensate for [8]. Extracorporeal treatments have the potential to exacerbate arterial hypotension. A study of 18 patients with alcoholic ACLF showed that treatment with MARS increased mean arterial pressure and systemic vascular resistance, but Prometheus did not [42]. The filtration step of Prometheus might have caused minor changes in colloid osmotic pressure, which blunted the potentially beneficial effects of vasodilator removal, resulting in a drop in mean arterial pressure [42].

MARS vs prometheus

Only one study compared the efficacy of MARS and Prometheus [42]. The study included 18 patients diagnosed with alcoholic cirrhosis and superimposed alcoholic hepatitis. These patients were randomly assigned to three groups: standard medical therapy (SMT) alone, SMT with MARS, or SMT with Prometheus. Both MARS and Prometheus treatments demonstrated noteworthy reductions in bilirubin levels. Nevertheless, the reductions observed with Prometheus were greater than those observed with MARS. In contrast, only MARS treatment exhibited improvements in mean arterial pressure and systemic vascular resistance [42]. Figure 1 illustrates the average reduction in bilirubin, ammonia, and creatinine levels, providing a more detailed comparison of MARS and Prometheus across all indications.

While MARS and Prometheus have been consistently effective in reducing bilirubin levels and improving hemodynamics, neither has shown a consistent survival benefit compared to standard medical therapy (SMT). A possible explanation for this is that both systems rely on albumin to bind circulating toxins, which may be compromised in the context of liver failure, resulting in limited detoxification capa-

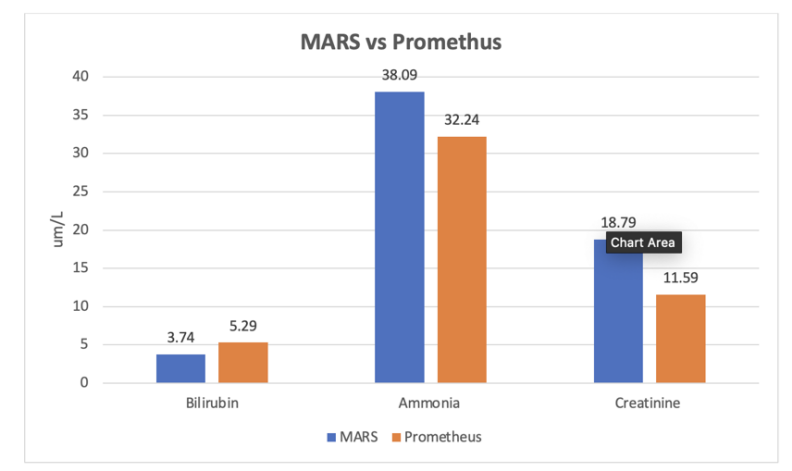

Figure 1: *A side-by-side comparison of the average decrease in bilirubin, ammonia, and creatinine levels for all indications with the use of MARS and Prometheus [6].*

bilities for these devices [43]. Additionally, the lack of improvement in patient survival is not surprising given the inadequate statistical power of the trials to examine this challenging clinical endpoint, especially in clinical contexts where acute illness severity and coexisting comorbidities are the dominant predictors of clinical outcomes. In addition, the insufficient reporting of adverse events across the trials has resulted in an incomplete safety analysis, further complicating matters. These findings underscore the importance of adequately powered trials and consistent reporting of adverse events for accurate evaluation of clinical outcomes and safety in medical research.

Conclusion

In summary, MARS and Prometheus are extracorporeal liver support systems designed to aid in the treatment of acute and chronic liver failure. MARS has been extensively studied and used for various liver pathologies, such as ALF, ACLF, HILI, PHLF, and DILI. Its effectiveness in removing water-soluble and lipophilic substances from the blood has led to improved patient outcomes, including reduced vasopressor support. However, further research is necessary to confirm its efficacy in improving patient survival. Prometheus also has demonstrated effectiveness in decreasing bilirubin levels and enhancing liver function in patients with ALF and ACLF. Additionally, it shows promise in improving transplant-free survival rates in ACLF. While both MARS and Prometheus have some complications, they are generally considered safe. Overall, these extracorporeal liver support systems serve as a valuable adjunctive therapy in managing liver failure. However, further research and greater accessibility are needed to determine their optimal use for various liver pathologies.

Conflict of Interest

None.

Bibliography

1. Adam René., *et al*. "Evolution of Indications and Results of Liver Transplantation in Europe. A Report from the European Liver Transplant Registry (ELTR)". *Journal of Hepatology* 57.3 (2012): 675-688.

2. Oketani Makoto., *et al*. "Changing Etiologies and Outcomes of Acute Liver Failure: A Perspective from Japan". *Journal of Gastroenterology and Hepatology* 26 (2011): 65-71.

3. Lee William M. "Etiologies of Acute Liver Failure". *Seminars in Liver Disease* 28.2 (2008): 142-152.

4. Bernuau Jacques., *et al*. "Fulminant and Subfulminant Liver Failure: Definitions and Causes". *Seminars in Liver Disease* 6.02 (1986): 97-106.

5. Jochmans Ina., *et al*. "Adult Liver Allocation in Eurotransplant". *Transplantation* 101.7 (2017): 1542-1550.

6. Tandon Radhika and Saied Froghi. "Artificial Liver Support Systems". *Journal of Gastroenterology and Hepatology* 36.5 (2021): 1164-1179.

7. Struecker Benjamin., *et al*. "Liver Support Strategies: Cutting-Edge Technologies". *Nature Reviews Gastroenterology and Hepatology* 11.3 (2014): 166-176.

8. Rifa Kinan Thomas Ernst., *et al*. "Prometheus--a New Extracorporeal System for the Treatment of Liver Failure". *Journal of Hepatology* 39.6 (2003): 984-990.

9. Mitzner Steffen R. "Extracorporeal Liver Support-Albumin Dialysis with the Molecular Adsorbent Recirculating System (MARS)". *Annals of Hepatology* 10.1 (2011): S21-S28.

10. Saliba Faouzi., *et al*. "Albumin Dialysis with a Noncell Artificial Liver Support Device in Patients With Acute Liver Failure". *Annals of Internal Medicine* 159.8 (2013): 522.

11. Ilonen Ilkka., *et al*. "Cytokine Profiles in Acute Liver Failure Treated with Albumin Dialysis". *Artificial Organs* (2007): 070802063815003.

12. Schmidt LE., *et al*. "Effect of Treatment with the Molecular Adsorbents Recirculating System on Arterial Amino Acid Levels and Cerebral Amino Acid Metabolism in Patients with Hepatic Encephalopathy". *Scandinavian Journal of Gastroenterology* 39.10 (2004): 974-980.

13. Camus Christophe., *et al*. "Liver Transplantation Avoided in Patients with Fulminant Hepatic Failure Who Received Albumin Dialysis with the Molecular Adsorbent Recirculating System While on the Waiting List: Impact of the Duration of Therapy". *Therapeutic Apheresis and Dialysis* 13.6 (2009): 549-555.

14. Larsen Fin Stolze., *et al*. "High-Volume Plasma Exchange in Patients with Acute Liver Failure: An Open Randomised Controlled Trial". *Journal of Hepatology* 64.1 (2016): 69-78.

15. MacDonald Andrew J., *et al*. "Use of the Molecular Adsorbent Recirculating System in Acute Liver Failure: Results of a Multicenter Propensity Score-Matched Study*". *Critical Care Medicine* 50.2 (2022): 286-295.

16. Sen Sambit., *et al*. "Pathophysiological Effects of Albumin Dialysis in Acute-on-Chronic Liver Failure: A Randomized Controlled Study". *Liver Transplantation* 10.9 (2004): 1109-1119.

17. Heemann Uwe., *et al*. "Albumin Dialysis in Cirrhosis with Superimposed Acute Liver Injury: A Prospective, Controlled Study". *Hepatology* 36.4 (2002): 949-958.

18. Bañares, Rafael Frederik Nevens., *et al*. "Extracorporeal Albumin Dialysis with the Molecular Adsorbent Recirculating System in Acute-on-Chronic Liver Failure: The RELIEF Trial". *Hepatology* 57.3 (2013): 1153-1162.

19. Vaid Arjun., *et al*. "Molecular Adsorbent Recirculating System as Artificial Support Therapy for Liver Failure". *ASAIO Journal* 58.1 (2012): 51-59.

20. Stutchfield BM., *et al*. "Systematic Review and Meta-Analysis of Survival Following Extracorporeal Liver Support". *British Journal of Surgery* 98.5 (2011): 623-631.

21. Liu Yong., *et al*. "[Artificial and Bioartificial Liver Support Systems for Acute and Acute-on-Chronic Liver Failure: A Meta-Analysis]". *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University* 29.8 (2009): 1529-1532.

22. Bañares Rafael Luis Ibáñez-Samaniego., *et al*. "Meta-Analysis of Individual Patient Data of Albumin Dialysis in Acute-on-Chronic Liver Failure: Focus on Treatment Intensity". *Therapeutic Advances in Gastroenterology* 12 (2019): 175628481987956.

23. Mitzner Steffen R., *et al*. "Improvement of Hepatorenal Syndrome with Extracorporeal Albumin Dialysis Mars: Results of a Prospective, Randomized, Controlled Clinical Trial". *Liver Transplantation* 6.3 (2003): 277-286.

24. Hassanein Tarek I., *et al*. "Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis". *Hepatology* 46.6 (2007): 1853-1862.

25. Parés Albert., *et al*. "Treatment of Resistant Pruritus from Cholestasis with Albumin Dialysis: Combined Analysis of Patients from Three Centers". *Journal of Hepatology* 53.2 (2010): 307-312.

26. Leckie P., *et al*. "Out-Patient' Albumin Dialysis for Cholestatic Patients with Intractable Pruritus". *Alimentary Pharmacology and Therapeutics* 35.6 (2012): 696-704.

27. Drolz Andreas., *et al*. "Extracorporeal Artificial Liver Support in Hypoxic Liver Injury". *Liver International* 31 (2011): 19-23.

28. Banayosy A El., *et al*. "First Use of the Molecular Adsorbent Recirculating System Technique on Patients with Hypoxic Liver Failure After Cardiogenic Shock". *ASAIO Journal* 50.4 (2004): 332-337.

29. Gilg S., *et al*. "Albumin Dialysis with Mars in Post-Hepatectomy Liver Failure (PHLF): Experiences from Two HPB Centers". *HPB* 18 (2016): e691.

30. Connor-Schuler Randi L., *et al*. "The Efficacy of Albumin Dialysis in the Reversal of Refractory Vasoplegic Shock Due to Amlodipine Toxicity". *Critical Care Explorations* 2.6 (2020): e0120.

31. Narayanan Mechu., *et al*. "The Efficacy of Albumin Dialysis in the Treatment of Severe Cholestatic Drug-Induced Liver Injury". *Critical Care Explorations* 4.8 (2022): e0752.

32. Eapen Jaishvi., *et al*. "The Efficacy of Extracorporeal Liver Support with Molecular Adsorbent Recirculating System in Severe Drug-Induced Liver Injury". *Oxford Medical Case Reports* 1 (2018): omx077.

33. Evenepoel Pieter., *et al*. "Prometheus Versus Molecular Adsorbents Recirculating System: Comparison of Efficiency in Two Different Liver Detoxification Devices". *Artificial Organs* 30.4 (2006): 276-284.

34. Ryska M., *et al*. "Fractionated Plasma Separation and Adsorption Significantly Decreases Intracranial Pressure in Acute Liver Failure: Experimental Study". *European Surgical Research* 42.4 (2009): 230-235.

35. Grodzicki M., *et al*. "Results of Treatment of Acute Liver Failure Patients with Use of the Prometheus FPSA System". *Transplantation Proceedings* 41.8 (2009): 3079-3081.

36. Rifai Kinan Anibh Das., *et al*. "Changes in Plasma Amino Acids During Extracorporeal Liver Support by Fractionated Plasma Separation and Adsorption". *Artificial Organs* 34.2 (2010): 166-170.

37. Oppert Michael., *et al*. "Extracorporeal Liver Support Therapy with Prometheus in Patients with Liver Failure in the Intensive Care Unit". *Therapeutic Apheresis and Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy* 13.5 (2009): 426-430.

38. Komardina Ekaterina., *et al*. "Prometheus Therapy for the Treatment of Acute Liver Failure in Patients after Cardiac Surgery". *Kardiochirurgia i Torakochirurgia Polska = Polish Journal of Cardio-Thoracic Surgery* 14.4 (2017): 230-235.

39. Evenepoel Pieter., *et al*. "Detoxifying Capacity and Kinetics of Prometheus--a New Extracorporeal System for the Treatment of Liver Failure". *Blood Purification* 23.5 (2005): 349-358.

40. Kribben Andreas., *et al*. "Effects of Fractionated Plasma Separation and Adsorption on Survival in Patients with Acute-on-Chronic Liver Failure". *Gastroenterology* 142.4 (2012): 782-789.e3.

41. Rifai Kinan Carsten Hafer., *et al*. "Treatment of Severe Refractory Pruritus with Fractionated Plasma Separation and Adsorption (Prometheus)". *Scandinavian Journal of Gastroenterology* 41.10 (2006): 1212-1217.

42. Laleman Wim., *et al*. "Effect of the Molecular Adsorbent Recirculating System and Prometheus Devices on Systemic Haemodynamics and Vasoactive Agents in Patients with Acute-on-Chronic Alcoholic Liver Failure". *Critical Care* 10.4 (2006): R108.

43. Matar Abraham J and Ram Subramanian. "Extracorporeal Liver Support: A Bridge to Somewhere". *Clinical Liver Disease* 18.6 (2021): 274-279.

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