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RESEARCH ARTICLE

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Impact of Covid-19 on the therapeutic plasma exchange service within the South East Asian region: Consensus recommendations and global perspectives

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Abstract

Introduction: Therapeutic plasma exchange (TPE) for neuroimmunological disorders has played an increasingly important role within the Southeast Asian (SEA) region. The South East Asian Therapeutic Plasma exchange Consortium (SEATPEC) was formed in 2018 to promote education and research on TPE within the region. The advent of the Covid-19 pandemic has produced challenges for the development and expansion of this service.

Methodology: A qualitative and semi-quantitative questionnaire-based survey was conducted by SEATPEC member countries from January to June 2020 (Phase 1) and then from July 2020 to January 2021 in (Phase 2) to assess the impact of Covid-19 on regional TPE.

Objectives: The study's main objectives were to explore the challenges experienced and adaptations/adjustments taken by SEATPEC countries in order to continue safe and efficient TPE during the Covid-19 pandemic.

Results: The pandemic was found to disrupt the delivery of TPE services in all SEATPEC countries. Contributing factors were multifactorial due to overstretched medical services, staff shortages, quarantines and redeployments, fear of acquiring Covid-19, movement restriction orders, and patient's psychological fear of attending hospitals/testing for Covid-19. All SEATPEC countries practiced careful stratification of cases for TPE (electives vs emergencies, Covid-19 vs non-Covid-19 cases). SEATPEC countries had to modify TPE treatment protocols to include careful preprocedure screening of patient's for Covid-19, use of personal protective equipment (PPE) and post-TPE sanitization of machines and TPE suites.

Conclusion: Based on the responses of the survey, SEATPEC countries produced a consensus statement with five recommendations for safe and effective TPE within the region.

KEYWORDS

Covid-19, impact, South East Asia, therapeutic plasma exchange

1 | INTRODUCTION

1.1 | Problem statement

The Covid-19 pandemic has disrupted all countries, societies health care systems, and services. The degree of socio-economic and psychological impact varies by region and populations.[1] In South East Asia (SEA) made up of 11 member countries with a population of over 600 million, the use of therapeutic plasma exchange (TPE) for both central and peripheral neuroimmunological disorders has been evolving and expanding rapidly over the last decade.[2,3] The South East Asian Therapeutic Plasma Exchange Consortium (SEATPEC) was established in 2018 to promote the clinical provision of education and research in TPE for neuroimmunological diseases regionally.[2,3] The Covid-19 pandemic poses unprecendented challenges for the development and expansion of this service.

However, the true impact of the pandemic on the delivery of hospital-based neuroimmunological TPE services is currently unknown within SEA. Preliminary reports from SEA suggest the redistribution of hospital and human resources to deal with the pandemic had led to temporary discontinuation of neurological TPE services in countries like Malaysia.[5] Therefore, investigating the impact of the pandemic on all countries within SEA needs to be ascertained so that country-specific/regional strategies and recommendations can be developed to optimize TPE service delivery during the pandemic and for future health system disruptions.

There are many unknowns with regards to the safety of elective and urgent use of TPE during the pandemic; further short-term and long-term impact of TPE and its timing with the advent of universal vaccination also needs consideration. This uncertainty exists due to a lack of available guidelines on the conduct of TPE during the pandemic for neurological conditions regionally and globally. Consensus statements by organizations such as the European Academy of Neurology (EAN) and the American Academy of Neurology (AAN) suggest careful consideration when starting immune depleting/modifying agents balancing between the risks of Covid-19 infections and the need for treatment.[6-8]

Similarly, neurologists and regional experts in SEATPEC share concerns about the need for screening of patient's prior to TPE, modification of TPE protocols to ensure the safety of patient's and operators, timing to vaccinations as well as the use of this technology in the treatment of neuroimmunological conditions in Covid-19 patients. TPE and convalescent plasma has also been postulated as possible treatment options in mild to severe Covid-19 patients.[4] To answer these questions, 25 clinicians and researchers from SEATPEC countries were engaged.

1.2 | Objective

The primary objective of this study was to identify the challenges faced by regional TPE services including describing the adjustments and adaptations needed to minimize service interruptions during the Covid-19 pandemic. The adaptations and best practices amalgamated to form targeted recommendations based on consensus amongst SEATPEC neurologists.

Secondary objectives were to report SEATPEC neurologists experience on the conduct of TPE and occurrence of Covid-19 infections in post TPE patients on follow-up from real-world observations and to see if any developed a severe type of Covid-19.

1.3 | Methodology

An explorative qualitative and semi-quantitative survey to study the impact of Covid-19 on TPE services within the SEA region was performed. The questionnaire was designed to address practical issues and explore several main themes experienced by TPE neurologists during the Covid-19 pandemic. The study was done in two phases; Phase 1 from 1st January to 30th June 2020 during the initial phase following the recognition of Covid-19 cases globally and the declaration of the pandemic by WHO and subsequently Phase 2 from 1st July to 31st January 2021 during the later phase of the ongoing pandemic.

The questionnaire was designed by a single Neurologist (SV) and administered to all neurologists who are members of SEATPEC. It comprised 12 questions in Phase 1, with Yes/No answers with explanations for the answers and 16 questions in Phase 2 with Yes/No answers and explanations where necessary. The survey was administered through email and a "Survey Monkey" web-based tool (see Questionnaires for Phase 1 and 2 of study under Supplementary files).

Ethical approval: This study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia as part of retrospective and prospective cross sectional data collection on TPE and neuroimmunological diseases under the Demyelinating disease database (DDD)}: NMRR 11-1049-10 503.

1.4 | Inclusion criteria

1. Twenty-one neurologists from 11 SEA countries and one from a South Asian country were contacted as members of SEATPEC. All were working at major referral centers with large neurology services dealing with neuroimmunological diseases and TPE.
2. Only neurologists who were performing TPE for neuroimmunological conditions on a routine basis with either a dedicated "in house team" or outsourced from the Hematology or Nephrology disciplines were included.

1.5 | Exclusion criteria

Not a SEATPEC member and not actively prescribing or performing TPE.

1.5.1 | Consent for participation

Verbal Consent through emails for the questionnaire-based interviews was obtained from all participating neurologist's prior to emailing the questionnaire/Survey monkey onwards.

1.5.2 | Duration of study

All responses were obtained from 1 January 2020 to 31 January 2021.

1.5.3 | Statistical analysis

Qualitative and semi-quantitative analysis was performed looking at absolute values and percentages.

2 | RESULTS

A.

i. Respondent details and scope of practice: (see Tables 1 and 2; Figure 1).
The results of the Survey are shown below. The questionnaires/survey monkey were filled up by respondents from eight countries within the SEA region and a South Asian country giving a 75% positive country responder rate. Respondents from three remaining countries (7) were unable to contribute despite email invitations. Fourteen out of twenty-one neurologists (66.7%) approached, participated in the survey. There were three neurologists from Singapore, two each from Malaysia, Thailand, and Myanmar and one neurologist each from Laos, Indonesia, Vietnam, Philippines, and Bangladesh, respectively. All 14 respondents were adult neurologists working at major tertiary referral centers.

ii. Awareness of Global, WHO, regional, or local generic guidelines prior to Survey:
Prior to the survey, all respondents acknowledged the lack of international or regional guidelines on the use of TPE during the pandemic for central and peripheral neuroimmunological disorders. All respondents were utilizing generic country-specific and WHO recommendations on preventive and precautionary measures modified to their local situation when dealing with possible or confirmed Covid-19 patients scheduled for elective or emergency TPE procedures.[5-18] All adhered to TPE indications as per ASFA 2019[18] (Table 1).

TABLE 1 Showing the total number of participating countries, neurologists, level of knowledge, and types of TPE used

Parameter	Phase 1 (Jan-June 2020) Number/percentage	Phase 2 (July-Jan 2021) Number/percentage
1. Total number of participating countries/n = 12	9/12 (75%)	9/12 (75%)
2. Total number of participating neurologists/n = 21	14/21 (66.7%)	14/21 (66.7%)
3. Awareness of Global or regional guidelines on TPE conduct during Covid-19 pandemic: Yes/No	Yes: 0 No: 14/14 (100%)	Yes: 0 No: 14/14 (100%)
4. Type of TPE being done		
• In house	4/9 (44%)	
• Outsourced to Nephrology/ Hematology departments	7/9* (56%) * (some who outsourced also did in house TPE)	
5. Type of TPE technology		
• Centrifuge technology	8/9 (89%)[a]	
• Membrane technology	8/9 (89%)[a]	
• Both	7/9 (78%)	
• Other types: Small Volume Plasma exchange	2/9 (22%)	

Abbreviations: n, number; Jan, January; TPE, therapeutic plasma-exchange.
[a]Some may be performing both centrifuge and membrane type of TPE with dedicated machines.

TABLE 2 Showing the total number of Covid cases during Phase 1 and 2 of the pandemic with the mortality rates

Country (ASEAN)	Total no. of cases (Jan-June 2020)	Mortality rates SEA (till June 2020) per million	Total No of Cases (July-Jan 2021)	Mortality rates, SEA (till 31 January 2021) per million	Total cases
Brunei	141	7	39	7.0	180
Cambodia	142	0	323	0	465
Indonesia	62 142	10.63	1 016 172	111.1	1 078 314
Laos	19	0	25	0	44
Malaysia	8658	3.88	206 301	22.98	214 959
Myanmar	313	0.11	139 832	0	140 145
Philippines	41 430	11.96	484 188	57.88	525 618
Singapore	44 664	4.63	14 872	5.17	59 536
Thailand	3190	0.84	15 592	1.1	18 782
Vietnam	346	0	1471	0	1817

Abbreviations: ASEAN, Association of South East Asian Nations; Jan, January; SEA, South East Asia; no., number.
Source: https://www.csis.org/programs/southeast-asia-program/southeast-asia-covid-19-tracker-0#trackers[19]

From 1 January 2020 to 31 January 2021, the status of Covid-19 cases and mortality rates as reported from ASEAN countries is as shown in Table 2.[19] There was a trend towards increasing number of cases and mortality rates in the latter half of the study. Postulated causes were human behavior with lack of observation of masking and social distancing in addition to relaxation of MCO's and increased human movement.[8,12,19]

B. For ease of review, the survey results are presented sequentially based on the questions and answers in the Questionnaire utilized for Phases 1 and 2 of the study (see Tables 3 and 4).

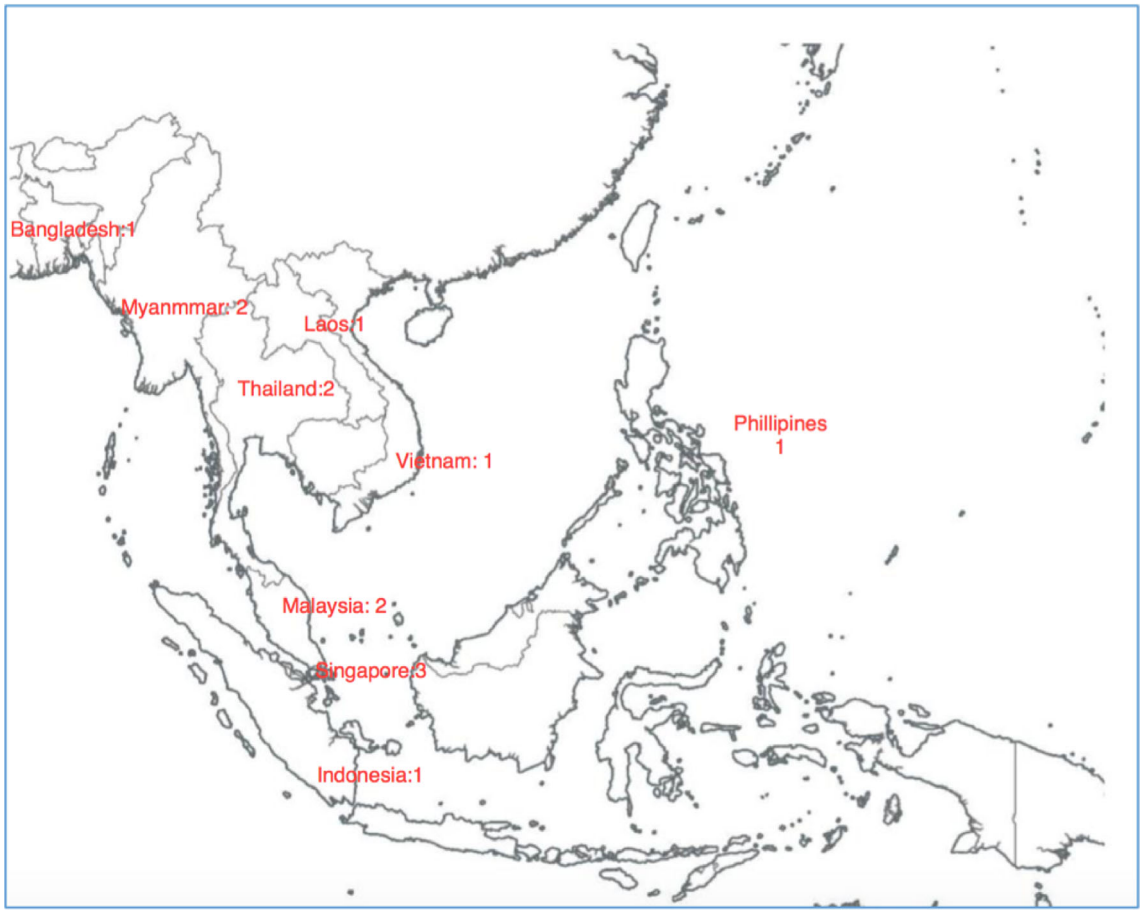

FIGURE 1 Showing the number of participating countries and the number of neurologists who answered the survey

TABLE 3 Results of the survey on health utilization, challenges of therapeutic plasma exchange during the Covid-19 pandemic and the impact of Sars CoV-2 on TPE services during Phases 1 (January 2020 to June 2020) and 2 (July 2020 to Jan 2021) of the pandemic

Questions/respondents, n = 14 or countries, n = 9	**Phase 1**	**Phase 2**
1. Do you have Covid-19 cases at your hospital? Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
2. Is your hospital a Covid-19/Hybrid Covid-19 Hospital? Y/N	Y: 11/14 (78.5%)	Y: 14/14 (100%)
3. Are you		
a. (i) Still referring NID (Neuroimmunological disease) cases for TPE? Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
(ii) Conducting Virtual Consultation* for TPE Counseling? Y/N	Y: 2/9 (14.2%) N: 7/9 (85.8%)	Y: 4/9 (28.5%) N: 5/9 (71.5%)
(n, no. of countries)		
(For Question 3b and c: see Table 1)		
4. Is there a drop/increase in TPE's between 2019 vs 2020/21?		
a. TPE patient workloads reduced (electives/ urgent) Y/N:	Y: 14/14 (100%)	Y: 14/14 (100%)
b. Percentage reduction in TPE workloads (range, %)		
0%-25%	7/14 (50%)	10/14 (71.4%)

(Continues)

TABLE 3 (Continued)

Questions/respondents, n = 14 or countries, n = 9	Phase 1	Phase 2
25%-50%	3/14 (21.4%)	2/14 (14.2%)
50%-75%	2/14 (14.2%)	1/14 (7.1%)
75%-100%	2/14 (14.2%)	1/14 (7.1%)
c. If still doing TPE, how many cases per year in 2020 till end Jan 21 vs 2019?	30% drop (229 cases vs 325 cases)	13% drop (286 vs 327 cases)
d. Percentage drop in number of cases 2019 vs 2020-till January 2021		22% drop (overall)
e. Commonest type of NID treated by TPE?		
• NMOSD and related disorders	30%	33%
• GBS (Covid-19 related and unrelated)	25%	22%
• MG	25%	22%
• AIE	15%	20%
• others	5%	3%
5. Still doing TPE for patients with or without Covid-19 and NID?		
a. Performing Elective TPE for Non-Covid-19 patients? Y/N	Y: 13/14 (92.8%) N: 1/14 (7.2%)	Initial phase: Y: 14/14, 100% Late phase: Y: 12/14, 87.5% (2 countries stopped for 2 months)
b. Performed TPE for Covid-19 related neurological complications: Y/N (active vs non active phase)	0	Y: 12/14, 87.5% during active phase Y: 2/14, 12.5% after day 10-14 post Covid-19 in non-active phase.
6. What factors have contributed to reduced TPE workloads?		
a. Patient-related factors: TPE patients fearful to come to hospital/do Covid-19 testing? Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
b. Shortage of Staff: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
c. Stratification of TPE cases; urgent vs non-urgent: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
d. Stratification of patients based on age &comorbidities: Y/N	Y: 5/14 (35.7%)	Y: 6/14 (42.8%)
e. Logistic Issues d/t MCO: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
f. Staff Fear of conducting TPE? Y/N	Y: 7/14 (50%)	Y: 7/14 (50%)
7. Have there been		
• Interruptions of supply of TPE consumables/ replacement fluids? Y/N	N: 14/14 (100%)	N: 14/14 (100%)
• Biomarker Access interruptions	N: 9/9 (100%)	N: 9/9 (100%)
• Biomarker Access Challenges? (in house/ outsourced) Y/N (n = 9)	Y: 8/9 (88.9%)	Y: 8/9 (88.9%)
8. Is it safe to continue TPE during the pandemic?		
a. Is it safe to continue TPE during pandemic: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
b. Do you feel TPE increases the risk of Covid-19 in pts? Y/N	N: 14/14 (100%)	N: 14/14 (100%)
c. Are there concerns about the cost of Covid-19 testing: Y/N	Y: 7/14 (50%)	Y: 4/14 (25%)
d. Have any patients with NID developed Covid-19 post TPE? Y/N (n = 14 respondents)	N: 14/14 (100%)	N: 13/14 (92.8%)

TABLE 3 (Continued)

Questions/respondents, n = 14 or countries, n = 9	Phase 1	Phase 2
e. With regard to timing of vaccination to TPE, to defer one month	Not applicable	Y: 14/14 (100%)
9. What precautions are taken prior to initiating TPE and during TPE?		
i. Pre TPE CSQ*: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
ii. Pre TPE Covid-19 screen with Covid-19 PCR/RTk antigen in all pre TPE pts: Y/N	Y: 8/14 (57.1%)	Y: 12/14 (85.7%) (Not 100% due to resource issues in some countries for PCR testing)
iii. Precautions taken during TPE: Mask, PPE, gloves, Face shield/Visor (PPE Level determined by if symptomatic or Covid-19 +ve/−ve): Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
iv. Screening of Plasma for Covid-19 antibodies: Y/N	N: 14/14 (100%)	N: 14/14 (100%)
10. Are alternatives to TPE used? Y/N (n:number of respondents)	Y: 11/14 (78.5%) N: 3/14 (22.5%)	Y: 12/14 (85.7%) N: 2/14 (14.3%)
i. State types: IVIG Y/N	Y: 11/14 (78.5%)	Y: 12/14 (85.7%)
ii. Others/No treatment: Y/N	Y: 7/14 (50%)	Y: 7/14 (50%)
11.		
i. Performing Convalescent Plasma: Y/N	N: 0/14	N: 3/14
ii. Affiliated to Global studies: Y/N	N: 0/14	N: 3/14
12. What is the impact of Covid-19 on regional TPE in the future?		
i. Change in TPE protocols with prescreening & PPE for Covid-19 exposure prevention: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
ii. Need for Covid-19 dedicated TPE machines/Covid-19 dedicated neurology wards: Y/N	Y: 7/14 (50%)	Y: 7/14 (50%)
iii. Modify timing of TPE to vaccination timing: Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
13. Would you be willing to participate in the development of a regional consensus recommendation for safe & efficient TPE? Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)
14. Do you agree that		
a. TPE may be offered to all patients regardless of whether Covid-19 positive or negative if	Y: 14/14 (100%)	Y: 14/14 (100%)
i. There are strong clinical indications for treatment (as per ASFA[18])		
ii. The treatment is urgent and cannot be delayed		
iii. There are no other alternatives for treatment		
iv. The center offering TPE is equipped with safe protocols to screen and protect against inadvertent transmission of SARS-CoV-2 viral infection. Y/N		
15. Do you agree that If non-urgent, TPE may be postponed until the patient is considered to be non-infective by local infectious disease consultations and country specific/WHO protocols? Y/N?	Y: 14/14 (100%)	Y: 14/14 (100%)

(Continues)

TABLE 3 (Continued)

Questions/respondents, n = 14 or countries, n = 9	Phase 1	Phase 2
16. Do you agree it is important to maintain safety of staff, TPE patients and caregivers prior to, during and post TPE with pre-procedure screening of all patients? Y/N	Y: 14/14 (100%)	Y: 14/14 (100%)

Abbreviations: ASFA, American Society For Apheresis; GBS, Guillain-Barre syndrome; IVIG, intravenous immunoglobulins; Jan, January; N, no; NID, neuroimmunological diseases; PCR, polymerase chain reaction; PPE, personal protective equipment; RTK, reverse transcriptase; TPE, therapeutic plasma exchange; Y, yes.

Question 1. Do you have Covid-19 cases at your hospital? Yes or No.

Question 2. Is your hospital a Covid-19 designated hospital/hybrid hospital? Yes or No.

78.5%, (11/14) of respondents during Phase 1 and 100% (14/14) of respondents during Phase 2 were either directly or indirectly involved in treating possible or confirmed Covid-19 patients with neurological disorders at their hospitals as a Covid-19 designated or hybrid Covid-19 hospital

Question 3.

a. (Tables 1 and 3).
   i. Do you still refer neuroimmunological cases for TPE during the pandemic at your hospital? Y/N.
   ii. Are these visits face to face visits or virtual visits for TPE counseling and decision making?
b. If yes, do you do "in-house Neurology based TPE" or is it outsourced to the Hematology or Nephrology departments?
c. What type of TPE is being used: Membrane filtration, centrifuge technologies, both or others? (Others: manual small volume TPE/limited plasma exchange).

(a) All respondents were still seeing patients with neuroimmunological diseases for possible TPE during Phases 1 and 2 albeit in reduced numbers due to general advice to minimize patient's exposure to possible Covid-19 infections by reducing elective non-urgent follow-ups. 14.2% and 28.5% of respondents during Phase 1 and 2, respectively, conducted virtual neurological visits for TPE counseling and planning via virtual platforms (telephone calls, whatsapp, face-time, emails, etc, eg, Malaysia) or modified tele-neurology visits (eg, Malaysia and Singapore) in the absence of established teleneurology portals in the former mainly in Phase 2.[5]

(b,c) TPE was conducted either as "In house Neurology based TPE" or outsourced to the Nephrology and Hematology departments. Types of TPE used included centrifuge (8/9, 89%), membrane filtration (8/9, 89%) or both technologies (7/9, 78%) using either dedicated centrifuge or membrane filtration machines or adapting a membrane column to a conventional renal replacement machine) (Table 1).[2,3] Two countries were utilizing alternative methods of TPE (2/9, 22.2%) such as small volume plasma exchange (SVPE) technology in addition to conventional TPE, that is, Myanmar and Bangladesh.

Question 4.

a. If still doing TPE, how many cases per year in 2019 versus 2020, is there are drop or increase? Explain in terms of percentages/absolute number of cases or ranges.
b. What were the commonest central and peripheral neuroimmunological conditions that required TPE? Explain.

In 2019, the total number of TPE cases reported by SEATPEC stake holders was 653 and in Phase 1 of 2020, there was a reduction of 30%, that is, 229 cases versus 325 cases in 2019, which rebounded in the second half of 2020 to January 2021 (286 vs 327 cases in 2019). Overall, compared with the previous year there was a reduction of 22%, with the majority reporting reductions from 0% to 50%. The four commonest neurological diseases treated were that of neuromyelitis optica spectrum disorders and related conditions, Guillain-Barré (Covid/Non-Covid related), myasthenia gravis, and autoimmune encephalitis (Table 3).

Question 5.

If Yes, still doing TPE, are you also doing TPE for Covid-19 patients with neurological complications? Y/N. Explain.

92.8% of the respondents surveyed (13/14) were still able to access and perform TPE either in house or outsourced to the hematology or nephrology units during early phase 1 of the Survey except for Malaysia, for non Covid-19 patients. In Malaysia, Neurology based TPE services was halted from March till May 2020 due to redistribution of beds and reassignment of health personnel including TPE staff to

Covid-19 related activities. Regionally, all respondents continued TPE with gradually increasing numbers during the early Phase 2 of the Survey except for Malaysia in late Phase 2 again due to increasing number of Covid-19 infections locally.

In Phase 1, none of the respondents had performed TPE for Covid-19 related central or peripheral neurological conditions. In Phase 2, 87.5% of respondents were treating Covid-19 patients with neurological conditions such as cerebrovascular events, Guillain-Barré syndrome (GBS), encephalitis, and acute disseminated encephalomyelitis TPE (personal communication from Malaysia, Myanmar, Indonesia, Singapore[9]). 87.5% of respondents were performing TPE for active Covid-19 infections with neurological complications during Phase 2 and the remaining 12.5% were performing TPE only for convalescent Covid-19 patient's (beyond the 14th day of infection) with Covid-19 or non-Covid-19 associated neurological central and peripheral neuroimmunological conditions.

None of the neurologists interviewed had reservations about treating these patients with TPE as all felt it was a basic human right as long as the indication as per ASFA was present.[18]

Question 6.

If not performing TPE at the moment or reduced number of TPE's performed, why has this occurred during the pandemic? Explain the factors causing this.

All respondents agreed that, TPE patient loads had reduced during Phases 1 and 2 of the Covid-19 pandemic due to multiple factors as described below;

i. Patient-related factors.
   Among the factors identified included the patient's fear of hospital exposure to Covid-19 and anxiety related to performing Covid-19 screening tests. Additionally, logistic issues due to movement control orders enforced by many countries also contributed to reduced TPE patient loads.
ii. Shortage of TPE Staff, human resource related factors and staff concerns:
   The main factor identified by all SEATPEC members (14/14, 100%) was the shortage of TPE staff consequent to the redistribution of TPE staff and doctors to help with the management of increasing Covid-19 wards and patients, clustering of cases among hospital staffs being exposed to positive patients/community spread, quarantine of staff in addition to logistic/transport issues due to movement control orders. Fifty percent of respondents also reported staff related fears of exposure to Covid-19 during the conduct of TPE but some felt this did not contribute to reduced patient loads.
iii. Other factors: Stratification of indication for TPE: Emergency versus Elective cases.
   Furthermore, reduction in TPE procedures/clinic attendance was done through careful stratification of TPE cases as either essential or non-urgent/electives which could be postponed or substituted with alternative therapies such as GBS, myasthenia gravis and neuromyelitis optica spectrum disorders (NMOSD) where other rescue treatment options exist such as intravenous immunoglobulins or steroids.
   This allowed for better utilization of staff, time and resources. A minority of respondents (35.7% and 42.8% in Phases 1 and 2, respectively) also stratified the use of TPE mainly to include the young rather than the elderly with multiple co-morbidities to avoid the risk of viral exposure to the latter group.

Question 7.

Have there been any issues with supply of TPE consumables, biomarker testing, or replacement fluids?

Reassuringly, none of the countries expressed problems with supply of consumables (standard centrifuge/membrane filter sets or replacement fluids that is, 5% albumin/fresh frozen plasma [FFP]) for standard TPE during this period. The main issue was the shortage of manpower to run the service.

In house, biomarker testing for a very limited panel of neuroimmunological antibody tests was currently only available in 4/9 countries (Malaysia, Singapore, Thailand, and Philippines) prior to the pandemic with all countries only having a limited panel for testing. The remaining countries (5/9) had to outsource this to country specific private/overseas commercial/academic laboratories of which non-reported any interruptions during the pandemic. So although, there were no interruptions to access, nearly all countries, 8/9 reported challenges in being able to ask for comprehensive biomarker testing panels for both common and uncommon auto-antibody panels for central and peripheral neuroimmunological disorders due to local inavailability and needing to outsource the service.

Question 8.

a. Do you think it is safe to perform TPE for neuroimmunological disorders during the Covid-19 pandemic?
b. Do you feel TPE increases the risk of Covid-19 in patients? Yes or No? Explain.
c. Have any of the patients with neuroimmunological disorders developed Covid-19 post TPE?
d. What about the timing of TPE and vaccinations?

a. Safety of TPE and confidence to continue TPE.
   All respondents felt that TPE was safe in patients with autoimmune neuroimmunological disorders in non-Covid-19/Covid-19 patients (during acute/post-convalescent period) in both phases of the Survey during the pandemic.
b. Risk of Covid-19 in planned TPE patients and vaccination.
   From a real world observational perspective, majority felt that TPE would not increase the risk of patients developing Covid-19 infection which seemed to be more dependent on exposure risk and local country-specific epidemiology. However, all acknowledged the need for more longitudinal data on this observation. All felt there was insufficient current evidence that TPE would reduce the immune responsiveness and ability for immune surveillance during the pandemic.
c. Occurrence of Covid-19 in post-TPE patients.
   Majority of the countries reported none of their post-TPE patient's developing Covid-19 during the last 11 months of the Survey except for Malaysia. In Malaysia, one patient with CRION with multiple co-morbidities including obesity, diabetes mellitus, and hypertension developed severe Covid-19 and died 2 weeks after TPE. However, in this patient the Covid-19 was deemed unrelated to the TPE but rather due to contact with community spread of Covid-19 and the multiple underlying co-morbidities. So 85% felt there was no data to suggest that TPE should be postponed during the pandemic for essential cases in the absence of other options. All respondents were unanimous, that TPE was an essential, vital service, lifesaving in some and did not increase the risk of developing Covid-19 post-procedure short term or long term.
d. Timing of vaccinations:
   All felt elective TPE should be delayed/postponed prior to and following vaccination by a month unless urgent to allow time for post vaccination immune response. For urgent TPE too, vaccination could be done 1 month after the TPE taking into consideration other factors such as patient's current state (for instance post-Covid-19 one month, free of active infection) and timing to certain immunosuppressant's (IS) (may be longer if IS such as anti-CD20s' have just been given) .

Question 9.

a. If still conducting TPE services, what precautions are being taken prior to, during, and post-TPE at your center?
b. Should replacement fluids be screened for Covid-19 antibodies?

(a, i) All respondents emphasized the need for proper precautions preprocedure, intraprocedure, and postprocedure which were more established in Phase 2.

(a, ii) Covid-19 screening questionnaires (CSQ) and Covid-19 testing.

Based on pre-screening protocols, patients at moderate to high risk were screened for Covid-19 using real-time PCR and/or rapid antigen test kits (RTK) depending on availability, cost and urgency of screening. In Phase 1, 57.1% of neurologists required a Covid-19 test to be done in all patients prior to TPE whether elective or emergent TPE especially if the CSQ was positive. The remainder only used the CSQ, testing when necessary.

In Phase 2 of the study, 85.7% of the respondents required a pre-TPE Covid-19 testing to be done especially if cases were from neighboring hospitals or areas of high Covid-19 prevalence even if they were asymptomatic. 25% of respondents were concerned about the cost of pre-screening Covid-19 tests especially PCR and relied on the CSQ pre-screening before making a decision on testing.

(a, iii) All respondents declared the importance of proper pre-screening utilizing country-specific Covid-19 screening questionnaires (CSQ) about Covid-19 symptoms/contact prior to the conduct of TPE, pre-procedure Covid-19 testing, the use of proper personal preventive equipment (PPE) for operators, intraprocedural care when dealing with blood spillages or contamination with secretions/aerosols in positive cases and post procedure sanitization of machines and TPE suites. Precautionary measures performed before TPE in all respondent's countries were generic with certain modifications according to country-specific and WHO recommendations. These included wearing surgical /N95 masks, visors, gowns with different levels of PPE, hand sanitization, gloves, and proper disposal of the PPE postprocedure for operators and mask wearing of TPE patients (where applicable) and caregivers.[10-13] No country had a dedicated machine for Covid-19 patients so postprocedure sanitization of the machine as per vendors/manufacturers requirements were essential[14,18] (see Tables 1 and 2).

(b) Screening of replacement products for Covid-19 antibodies.

Most SEATPEC tertiary centers adhered to standard international guidelines on the suitability of donors for blood donations and the use of FFP or albumin as replacement fluids as advocated by local blood bank agencies, FDA, and WHO. None were screening replacement products for SARS-CoV-2 antibodies.[15,16]

Question 10.

What alternatives to TPE are you using?

About 70% to 80% of respondents mentioned the availability of alternatives to standard TPE such as intravenous

immunoglobulin (IVIG) in phases 1 (78.5%, 11/14) and 2 (85.7%, 12/14). In other countries, where IVIG access was limited, alternatives to conventional TPE such as small volume plasma exchange (SVPE) or supportive therapies only were provided in the absence of other options.

Question 11.

a. Are you doing convalescent plasma therapy (CPT) for Covid-19 patients?
b. If not doing it, what are the barriers to performing this? Explain.
c. Is your center affiliated with any global study or registry on the use of convalescent plasma in patients with Covid-19 infections? Explain. If not, what are the barriers to participating?

All respondents had no experience at their center in using CPT for treating patients with severe Covid-19 with or without neuroimmunological complications during phase 1 of the study. The main reasons for this was the lack of experience using this type of treatment and the lack of current data at that time on the safety and efficacy of such a procedure.

However, in Phase 2 of the study, respondents from Myanmar, Indonesia, and Philippines were directly participating sites in global multicenter trials using CPT for 20% to 30% of their patient pool in patients with severe Covid-19 (personal communication from Myanmar, Indonesia, and Philippines).

Question 12.

Will the Covid-19 pandemic.

a. change your practice of TPE in the future and.
b. what is the impact of the pandemic on future development plans for TPE in your country and the region?

(a, i) Impact of Covid-19 on TPE.

All respondents felt the Covid-19 pandemic would have an impact on the future conduct of TPE due to the need for training of staff, risk mitigation strategies with pre-screening of patients for symptoms of Covid-19, pre-procedure testing for Covid-19, PPE for healthcare workers performing TPE in positive/suspected urgent cases and rigorous postprocedure machine sanitization. Some (50%) also suggested the future need for dedicated TPE machines and suites for Covid-19 positive cases.

(a, ii) Timing of TPE in Covid-19 positive/negative cases with neurological complications and the need for specialized Neuro-Covid-19 wards.

The timing of patients who are Covid-19 positive/negative for elective or emergency TPE would need to be planned well to minimize the risk of exposure/spread and optimize human and physical resources. Herewith 50% of respondents suggested the need for specialized neuro-Covid-19 wards to combat the present and future pandemics.

(a, iii) Timing of TPE with regard to vaccination.

Timing of TPE to vaccination schedules would also need careful deliberation (see above comment).

(b) Impact of Covid-19 pandemic on the future development plans and SEATPEC recommendations for regional TPE.

All respondents agreed that once the regional and global Covid-19 outbreak had stabilized all countries would be planning the future development, research and expansion of TPE services (conventional/alternative methods), improving staff trainings and developing country-specific protocols on safe TPE administration.

This survey served as a basis for all 14 participating members to produce recommendations for regional TPE conduct during Covid-19 which was unanimously agreed upon. (See Questions 13 to 16, Tables 3 and 4). The SEATPEC panel members identified key concerns about TPE management during the pandemic. Five statements and recommendations were drawn up and reviewed via emails achieving agreement via consensus. When there was ≥75% strong agreement with the recommendation, it was accepted and incorporated. (Table 4 and discussion).

3 | DISCUSSION

3.1 | Summary of results and global comparisons

This multicenter regional survey provides valuable insights into the impact of Covid-19 on the provision of TPE services to patients with neuroimmunological

TABLE 4 Showing SEATPEC degree of polled participant agreement with recommendations for conduct of TPE during and/post-Covid-19 pandemic based on Questions 13 to 16

Recommendations	Degree of virtual polled participant agreement (%)
Consensus Recommendation 1	14/14 (100%)
Consensus Recommendation 2	14/14 (100%)
Consensus Recommendation 3	12/14 (85.7%)[a]
Consensus Recommendation 4	14/14 (100%)
Consensus Recommendation 5	14/14 (100%)

Note: >75% degree of polled agreement was taken as positive consensus for the recommendation.

[a]Uncertainty here was due to concern among some members about the type of screening test used in view of existing resources, that is, with regard to RTK antigen/the more expensive and time consuming Covid-19 PCR test in all patients going for TPE whether symptomatic or not.

diseases within SEATPEC countries. Regional neurologists discussed strategies to overcome the challenges, in order to continue this essential service in a safe and effective manner. There were several universal themes. We observed that regional TPE services were affected by fluctuating patient loads (22% reduction regionally), as well as staff shortages due to redeployment of human and physical resources to Covid-19 related services. There was also a need to stratify essential/emergent TPE based on clinical urgency, patient age as well as premorbid state and co-morbidities.

Additionally, MCO, logistics, quarantine of staff, and psychological impact of Covid-19 on staff and patients were other issues that had to be addressed. The psychological impact of fear of transmission of the SARS-CoV-2 virus through attending hospital visits and of testing for Covid-19 was reflected in fewer patient hospital attendances in the initial phase of the outbreak. Though very few global studies have explored the impact of SARS-CoV-2 on TPE, a recent single center Italian study, showed similar findings of restratification of TPE need and reduced TPE procedures/number of patient's treated by 20% during the 2020 pandemic.[15]

SEATPEC neurologists also reiterated the need for stringent pre-screening and intra-procedural preventive precautions for Covid-19 in patient's undergoing TPE which mostly followed their country-specific hospital guidelines. Additionally, stringent PPE application during TPE and sanitization of the machines were mentioned as per manufacturer requirements.[17]

SEATPEC neurologists continue to modify their treatment schedules, realign their resources and have instituted important risk mitigation protocols in dealing with the impact of Covid-19 to their services. A number are seeing neurological complications with Covid-19 requiring IVIG/TPE, though numbers are still small.(Table 3)[9] Others, had to halt treatment for neurology based cases during phase 1 and late phase 2 of the pandemic with substitution of therapies with IVIG for both Covid-19 positive and negative patients with neurological issues.[5,9] These measures echo steps suggested in an editorial by Vossoughi et al. on the management of TPE during Covid-19 urging good pre-procedure assessments, flexibility, creative scheduling, adherence to good PPE practices, and strict cleansing of the TPE apparatus.[14]

It was reassuring to see that all SEATPEC members reiterated their commitment towards treating patients with neurological diseases that require TPE during the Covid-19 pandemic. All SEATPEC members were unanimous that stringent protocols had to be instituted and adhered to, in order to avoid inadvertent patient exposure to the SARS-CoV-2 virus during the pandemic. Many had reported using TPE in Covid-19 positive patients with neurological complications similar to anecdotal reports of TPE in combination with steroids/IVIG with good outcomes in Covid-19 associated meningoencephalitis, transverse myelitis, acute necrotizing encephalopathy, and acute axonal motor neuropathy.[19-21]

During the survey, the majority of SEATPEC members reported the absence of post-TPE patient's developing severe Covid-19 infections on follow-up except for the Malaysian patient who concomitantly had multiple co-morbidities. This purely observational real world report suggests indirectly the safety of TPE during the Covid-19 pandemic. EAN in its consensus statement, expressed confidence with regard to the use and safety of IVIG and TPE during the current pandemic stressing the lack of evidence to suggest that IVIG or TPE predisposed patients to Covid-19[6] Though no interruptions in access to consumables were reported, challenges existed in terms of availability of comprehensive biomarker testing pre and post pandemic in many SEATPEC countries.[2,3] More needs to be done to improve biomarker availability regionally through local expertise that is comprehensive and cost effective.[2,3] Timing of vaccinations and delaying it by a month or more pre or post TPE was also advised to allow for development of antibody response to the vaccines.

The role of convalescent plasma treatments (CPT) for patients with Covid-19 related complications was also emerging in certain SEATPEC countries though not exclusively for neurological complications. Not all SEATPEC members had experience or were comfortable recommending CPT. Evidence for utility of CPT is undergoing global evaluation.

3.2 | SEATPEC consensus recommendations

Based on these results through web based discussions amongst the 14 participating neurologists the following consensus recommendations and algorithm tailored to each SEATPEC country based on nearly 100% participant agreement was reached except with regard to testing for Covid-19 in all patients prior to TPE due to cost issues. These recommendations would be reviewed in the future as new evidence emerges and members agreed to audit the effectiveness of these recommendations with time (see Table 4 and Figure 2).

3.2.1 | Consensus recommendation 1

TPE may be offered to all patients regardless of whether Covid-19 positive or negative if

I. There are strong clinical indications for treatment (as per ASFA[18]).
II. The treatment is urgent and cannot be delayed.
III. There are no other alternatives for treatment.

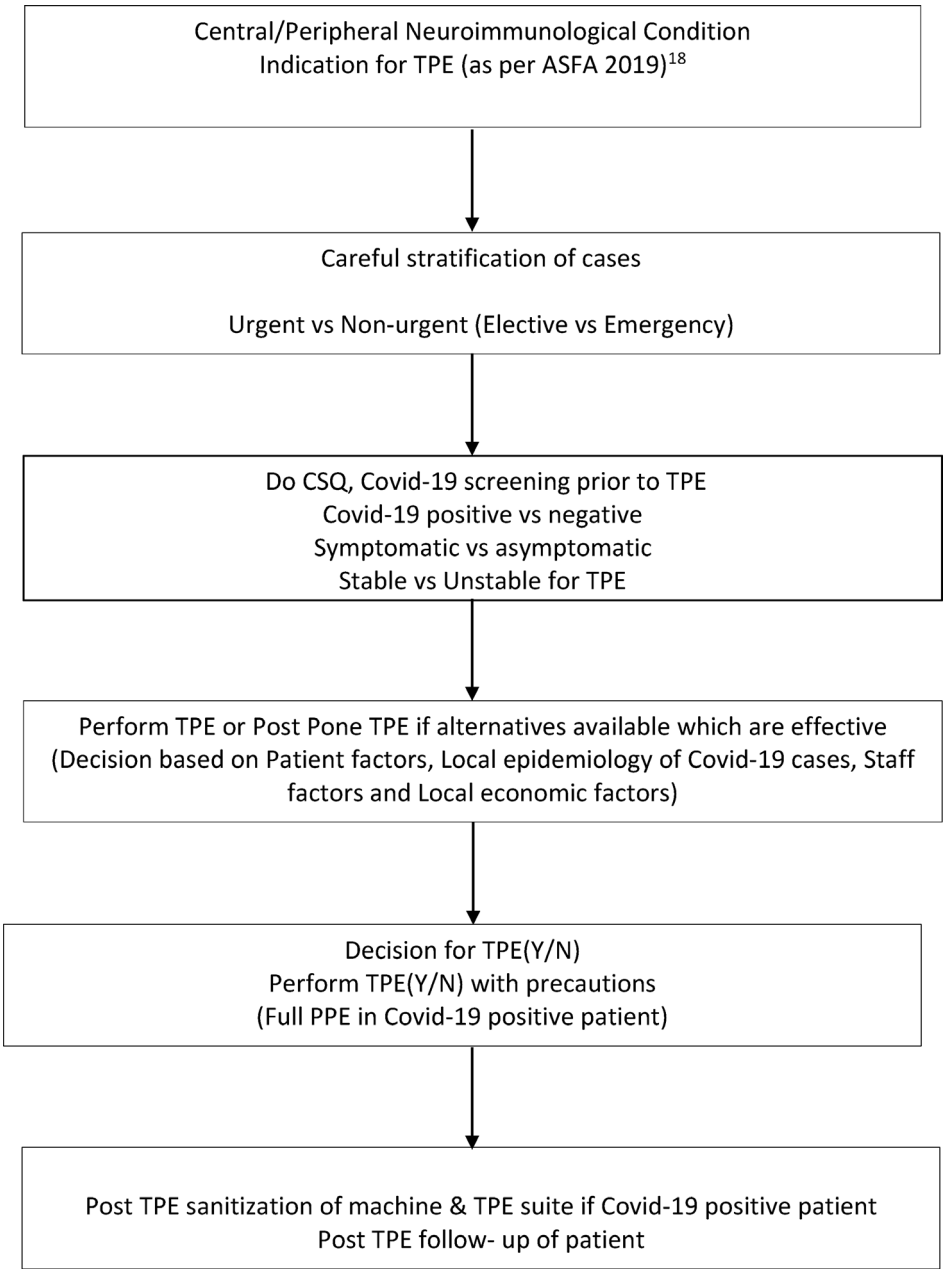

FIGURE 2 Proposed algorithm for referral and stratification of cases for TPE during the COVID-19 pandemic in SEATPEC countries for neurological indications

IV. The center offering TPE is equipped with safe protocols to screen and protect against inadvertent transmission of SARS-CoV-2 viral infection.

3.2.2 | Consensus recommendation 2

Indications for TPE in Covid-19 positive patients with neurological complications may follow generic indications as per ASFA, depending on urgency as assessed by respective clinicians and best medical practice. If non-urgent, TPE may be postponed until the patient is considered to be non-infective by local protocols/infectious disease consultations and country specific/WHO protocols.[8,14]

3.2.3 | Consensus recommendation 3

Depending on the prevailing local epidemiology of cases, careful allocation of essential TPE staff and resources for urgent elective and emergency TPE procedures should be managed subject to local conditions.

3.2.4 | Consensus recommendation 4

It is important to maintain safety of staff, TPE patients and caregivers prior to, during and post TPE. Pre-procedure screening of all patients with the Covid-19 screening questionnaire (CSQ), Covid-19 screening,

where possible with SARS-coV-2 PCR (preferable) or RTK antigen is important. Additionally, masking of patients where possible, limiting caregiver visits and post TPE patient surveillance for Covid-19 is important.[22]

3.2.5 | Consensus recommendation 5

Operators should receive adequate training on the level of PPE including donning and doffing techniques required for Covid-19 suspected or positive patients with training on protocols for post-TPE sanitization of machines (as per manufacturer requirements).

4 | CONCLUSION

This SEATPEC survey and recommendations provides important objective evidence on the use of TPE during the current pandemic within SEA adhering to current indications by ASFA for TPE in neurological conditions which will be audited in the future.[17] We acknowledge the limitations of this study in that not all SEATPEC members participated, the paucity of TPE and Covid-19 trials within the region and the constantly evolving pandemic. Nevertheless, these recommendations act as a guide for the safe conduct of neurology based TPE currently within SEA. SEATPEC hopes to continue to review and improve this document periodically, basing our recommendations on the latest and most robust evidence.[23]

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CONFLICT OF INTEREST

With regard to the contents, recommendations and drafting of this manuscript, all authors of SEATPEC have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

Viswanathan Shanthi: Conceptualization, methodology, data acquisition/curation, visualization, investigation, analysis, writing, drafting, review and editing of manuscript. Review for intellectual content, editing, writing: All other members of SEATPEC. Supervision: All other members of SEATPEC. Anupam Chhabra, Terumo Blood and Cell Technologies contributed to grammar checking of manuscript and Survey Monkey adaptation of questionnaires.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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