Acute on Chronic Liver Failure—What is in a ‘Definition’?

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Acute on chronic liver failure (ACLF) is a recently recognized syndrome and its definition has been evolving over last two decades. Currently, there is no universal consensus about the definition as kind of cases being seen in the Western world appear to be somewhat different from those that are seen in Asia Pacific region. But every one agrees that definition of ACLF should include following components. (a) The status of pre-existing liver disease, (b) defining the acute insult that leads to rapid deterioration of liver status, (c) time frame during which the acute insult can lead to rapid deterioration, (d) the quantification and definition of liver failure status after deterioration, which will determine the severity of ACLF, and (e) prediction of prognosis after analyzing first four components in the short and long terms. There is some consensus that number of organ failures may be the main determinant of prognosis. Whatever the definition is being used, the central role that superadded infections play in ACLF cannot be denied and need to be tackled aggressively. Apart from that, recovery may be possible if the acute insult or the baseline disease is curable, i.e. with the use of nucleoside analogs for hepatitis B, and corticosteroids for severe autoimmune hepatitis. Development of dynamic criteria with observations in Hospital may improve our understanding of prognosis as well as our approach to the management of ACLF. (J CLIN EXP HEPATOL 2016;6:233–240)

Arriving at a universal consensus on definition of liver failure has always been difficult. Earlier, East and West could never agree on a common definition for acute and subacute hepatic failure.^{1–5} The new kid on the block, acute on chronic liver failure (ACLF) seems to have inherited all of that and more.⁶ The term ACLF was possibly first used way back in early 1990s and denoted two components of same disease—a preexisting chronic liver disease with superadded acute deterioration brought on by a precipitating event.⁷ Since then, there have been several attempts to define it and a consensus is still eluding as is evident from Table 1.^{7–31} Earlier controversies about acute and subacute liver failure were primarily related to the timing of various manifestations of liver failure (Figure 1). Experts, from Indian subcontinent at that time, were seeing a lot of patients with ascites as the main manifestation of liver failure in the course of viral hepatitis and wanted to reserve the term of sub acute hepatic failure for it, while the

Western World hardly ever saw a similar case. Over time, even in India, the frequency of such presentation has gradually declined and many presume that this entity was nothing but a presentation of ACLF. Whether all cases of subacute hepatic failure were caused by acute hepatitis super-added on chronic liver disease without cirrhosis (Type-A, ACLF as per WGO classification²⁹ or recently described compensated advanced chronic liver disease or cACLD³²) remains to be determined. In those days, it was not possible to diagnose cACLD, as there was no transient elastography available and trans-jugular liver biopsies were not routinely done in Indian subcontinent.

As the term implies, the definition should define a disease with high specificity and sensitivity. Diagnostic criteria should be objective and cover the whole range of liver failure cases. It should be possible to select cases prospectively using the diagnostic criteria. At the same time, the criteria should be validated in different cohorts of patients. Ideally, when diagnostic criteria are met, the disease should be ACLF and nothing else. Not only that, as classified by definition, it should be possible to predict the outcome. In relation to ACLF, definition will need to have several components, for example:

- First component is pre-existing chronic liver disease and its severity should be specified if possible as it is likely to impact the ultimate outcome. There has been an attempt to classify first component by WGO group into subtypes A, B and C²⁹ depending on severity of pre-existing liver disease.
- Second component is acute insult and they can differ in severity as well as type. There have been various ways to sub-classify this event but it is important to spell out not only the severity of this component but also the potential of

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Abbreviations: ACLF: acute on chronic liver failure; ASA: American Society of Anesthesiologists; INASL: Indian Association for study of the liver; MELD: Model for End-Stage Liver Disease; NACSELD: North American Consortium for Study of End Stage Liver Disease; SBP: spontaneous bacterial peritonitis; SOFA: Sequential Organ Failure Assessment
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Table 1 Various Definitions of Acute on Chronic Liver Failure Used in Literature.

S. no.	Author	Acute insult	Chronic disease	Signs of failure	Appeared after how much time of acute insult	Increased mortality during how much time	Basis
1	Ohnishi et al. ⁷	Precipitating events	Ongoing liver disease	Deterioration	Not defined	Not defined	Arbitrary
2	Yang et al. ⁸	Acute hepatitis	CH B	ALT > 10 × ULN, Bilirubin > 15 mg/dL, prolonged PT > 5 s and HE	Not defined	Not defined	Arbitrary
3	Jalan and Williams ⁹	UGI Bleed	Well compensated CLD	Renal dysfunction of HE	Not defined	Not defined	Arbitrary
4	Sen et al. ¹⁰	Inflammation-related precipitant (infection or alcoholic hepatitis) or UGIB	Cirrhosis	Increasing jaundice (Bilirubin 6 mg/dL or more) and either HE (Grade 2) or HRS	2–4 weeks	Not defined	Arbitrary
5	Wasmuth ¹¹	Not defined	Liver cirrhosis based on a histopathological diagnosis or compatible laboratory data and sonographic findings	Jaundice, ascites, hemodynamic instability and/or HE grade III–IV compatible with the definition of hepatic decompensation necessitating further treatment in the ICU	Recent	Not defined	Arbitrary
6	Yu et al. ¹²	Acute or subacute hepatitis	Hepatitis B or C carrier, chronic hepatitis or cirrhosis	Bilirubin > 10 mg/dL, Ascites, HE > Grade 2 and prolonged PT (PTI < 40%)	2 weeks to 6 months	Not defined	Arbitrary
7	Laleman et al. ¹³	Alcoholic hepatitis	Alcoholic cirrhosis	Persistent deterioration despite treatment with bilirubin > 12 mg/dL	Not defined	Not defined	Arbitrary
8	Wang et al. ¹⁴	Acute decompensation	CLD	Severe liver dysfunction, HE grade 2 or higher	Not defined	Not defined	Arbitrary
9	Sarin et al. (APASL) ¹⁵	Hepatotropic viruses, Other viruses, bacterial infection and sepsis, alcohol and other toxins, variceal bleed, HBV flares	NAFLD, NASH, Chronic hepatitis, Undiagnosed cirrhosis, known jaundice and coagulopathy, compensated cirrhosis, decompensated cirrhosis	Jaundice and coagulopathy followed by ascites and/or HE	4 weeks	Not defined	Arbitrary
10	Krishna et al. ¹⁶	Acute Hepatitis A or E	Cirrhosis	A high SOFA/APACHE II score with jaundice and either HE or renal failure	2–4 weeks	Not defined	Arbitrary
11	Sun et al. ¹⁷	Decompensation	CLD	Severe debilitation and dysfunction of the alimentary tract, with Bilirubin > 10 mg/dL or an increase of Bilirubin > 10 mg/dL/day; and PTI < 40%	Not defined	Not defined	Arbitrary
12	Shi ¹⁸	Acute deterioration	CLD	Bilirubin > 10 mg/dL, PTI < 40%, ascites and or HE	Not defined	Not defined	Arbitrary
13	Novelli et al. ¹⁹	Acute deterioration	CLD	Increasing jaundice	Not defined	Not defined	Arbitrary
14	Katoonizadeh et al. ²⁰	Acute hepatic insult	Compensated CLD with Bilirubin > 5 mg/dl (without extrahepatic obstruction)	Rise in bilirubin levels by >50% or up to 20 mg/dl, or HE more than grade 2, or fresh development of ascites and or HRS	4–8 weeks	Not defined	Arbitrary
15	Karvellas et al. ²¹	Not defined	Cirrhosis	Decompensation such as variceal bleed, HE, HRS, MOF requiring organ support	Not defined	Not defined	Arbitrary
16	Zhai et al. ²²	Acute deterioration	Compensated CLD, chronic hepatitis B or hepatitis B virus carriers	HE, ascites, bleeding, or HRS	Not defined	Not defined	Arbitrary
17	Zhihui et al. ²³	Not defined	CLD	Recent development of bilirubin > 10 mg/dL and PTI < 40%, HE (grade 2 or more),	Not defined	Not defined	Arbitrary

(Continued on next page)

Table 1 (Continued)

S. no.	Author	Acute insult	Chronic disease	Signs of failure	Appeared after how much time of acute insult	Increased mortality during how much time	Basis
19	Huang et al. ²⁴	Acute hepatic insult	CHB/cirrhosis	Jaundice and coagulopathy, complicated with ascites and/or HE with bilirubin 10 mg/dL (or more) and PTI 40% or less.	4 weeks	Not defined	Arbitrary
20	Olson et al. ²⁵ (Working Group EASL and AASLD)	Precipitating event	CLD	Acute deterioration with MOF	Not defined	3 months	Working definition at the formation of research consortium a research consortium to advance the state of the science of acute-on-chronic liver failure by the American Association for the Study of Liver Disease and the European Association for the Study of the Liver
21	Wlodzimirov et al. ²⁶ (Systematic Review)	Precipitating event	Pre-existing CLD	Acute deterioration with MOF (73 prognostic indicators analyzed)	Not defined	Not defined	Systematic Review
22	Moreau et al. ²⁷ (EASL CLIF Consortium)	Acute decompensation (ascites, encephalopathy, UGIB or infection)	Cirrhosis	Organ failures in ACLF defined: Liver-Bilirubin 12 mg/dL or more; Kidney-creatinine 2 mg/dL or more; cerebral-HE grade 3 or 4; Coagulation-INR > 2.5 and/or platelets <20,000 dL ⁻¹ ; circulatory failure use of inotropes and respiratory failure PaO ₂ /FiO ₂ 200 or less or sPO ₂ /FiO ₂ less than 214 (ACLF classified in to 3 grades)	Not defined	28 day	Based on Study of 1343 patients of which 415 had ACLF at 29 centers
23	Bajaj et al. ²⁸ NACSELD	Acute deterioration— infection	Cirrhosis	Two or more extrahepatic organ failure	Not defined	Not defined	Based on Study of 507 patients in 18 centers
24	Jalan ²⁹ WGO Working Party	Precipitants: virus, drugs, alcohol, ischemia, surgery, sepsis, idiopathic	Type A: CLD but no cirrhosis; Type B: Compensated cirrhosis; Type C: Decompensated cirrhosis	Hepatic and extrahepatic organ failure	Weeks (to be defined by data)	Up to 3 months	Arbitrary
25	Sarin ³⁰	Hepatic insult: ethanol, hepatitis B reactivation, viral hepatitis, autoimmune hepatitis, drug-induced liver injury, Wilson's disease flare, variceal bleeding Unknown	CLD, cirrhosis— asymptomatic, compensated, no prior decompensation	Bilirubin > 5 mg/dL, coagulopathy INR > 1.5, ascites or HE	4 weeks	4 weeks	An attempt to validate and fine tune the 2012 definition on basis of APASL ACLF Research Consortium database findings.
26	Shalimar ³¹ INASL Consortium for ACLF Research in East Experience	As per APASL definition 2009	As per APASL definition 2009	As per APASL definition 2009	As per APASL definition 2009	As per APASL definition 2009	Data analysis of 1049 Patients from 10 centers in India supported use of extra hepatic insults as precipitants

ACLF, acute on chronic liver failure; CHB, chronic hepatitis B; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; PT, prothrombin time; PTI, prothrombin time index; CLD, chronic liver disease; ICU, intensive care unit; MOF, multiple organ failure; SBP, spontaneous bacterial peritonitis; INR, internationalized ratio.

Figure 1 Timing of events in acute liver failure, sub acute liver failure and acute on chronic liver failure. Modified from Ref.¹⁵

reversibility with treatment. Latter will be more difficult to assess. One could classify precipitating factor as per pathophysiology as³³:

- (i) Type-1: Non-hepatic insults such as severe sepsis, pancreatitis or gastrointestinal bleeding
- (ii) Type-2: Hepatic injury, which can be further sub-classified as

2a: Acute viral hepatitis, which is common in this subcontinent.³⁴

2b: Other causes of hepatic inflammations such as drug induced liver injury, flare of autoimmune hepatitis or Wilson's disease and various infections causing liver inflammation

2c: Loss of hepatocytes leading to acute worsening such as hepatic resection, trans-arterial chemoembolization, radiofrequency ablation or ischemia/tumor of liver.

- (c) Third component should be time frame during which acute event leads to liver failure.
- (d) Fourth component should be definition and quantification of deterioration of liver functions or defining the failure that has been brought on by the acute precipitating event. Current severity of liver failure is the most objective data available at the time of presentation as the state of pre-existing liver disease may not be known to the attending clinician. Whether this can predict outcome more accurately rather than the first two components will have to be analyzed by the future studies. The CANONIC study seems to suggest that among patients with ACLF, the prognosis depended on factors independent of the precipitating events.²⁷ and
- (e) Last component should give us information about prognosis in such a case or predicted outcome, which should be validated in independent studies. Currently available data support higher mortality in 28-day as well as 90-day period.³⁵

Table 1 lists all these components of the definitions used so far. In this connection it is important to realize that ACLF is a dynamic syndrome. Quite often, at the time of a patient coming under observation, the severity of liver failure may be evolving. Patient may have just begun to deteriorate or he may already be on the road to recovery. There may be nearly 50% chance of improving as well as deteriorating, and most

prognostic models such as Model for End-Stage Liver Disease (MELD) or CLIF-Sequential Organ Failure Assessment (SOFA) score or are based on one-time observation on admission. Dynamic assessment over a period of time is likely to predict outcome more accurately rather than one-time assessment. One such model for acute liver failure is already popular in this part of the world.³⁶

Gustot et al.³⁵ assessed ACLF grades at different time points to define disease resolution, improvement, worsening, steady or fluctuating course among 388 patients with ACLD over 7 months period. They found that ACLF resolved or improved in 49.2%, had a worsening, steady or fluctuating course in 30.4% and worsened in 20.4% of patients. They identified 12 different patterns of early (up to 28-days) clinical course of ACLF and found that mortality was closely determined by the final grade of ACLF and not by the first assessment. Their findings suggest that the best time point to define the clinical course of ACLF was between the third and seventh days after ACLF diagnosis/admission. During this period, therapeutic intervention in patients with ACLF should be directed not only to improve the organ failures present at diagnosis, but also to prevent impairment of function of the other organs during hospitalization. Such an analysis can also aid in decisions about liver transplantation on one hand and about futility of care on the other.

With this background, we analyze different definitions of ACLF and whether unification is possible. Majority of papers listed in Table 1 have used arbitrary definitions which are not based on observed data and will not be discussed here. Three main exceptions are the working groups in US, Europe and Asia-Pacific definition,^{27,28,30} who have analyzed a large number of patients to come to a consensus definition which is also being revised as and when additional data become available. Here again NAC-SELD (North American Consortium for Study of End Stage Liver Disease) approach is somewhat similar to that

of EASL because both believe that poor outcome is best predicted by extra-hepatic organ failure.³⁷ Only they find CANONIC use of CLIF-SOFA a little cumbersome and would prefer a definition of organ failure that can be easily used at bedside. Definition offered by APASL is different from the Western definition and such divergent definitions possibly reflect different profile of patients being seen in different geographical regions.^{15,30}

Sarin and Choudhury⁶ have recently summarized main differences between EASL-AASLD definition and APASL definition of ACLF. Both have accepted that ACLF behaves differently from ALF, is associated with organ failure and sepsis, and is associated with high mortality within short period of few weeks and hence these patients may be candidates for liver transplantation.

EASL-AASLD definition is based on study of patients frequently seen in the western World and it has excluded WGO type A cases²⁹ from underlying chronic liver disease. It recognizes both hepatic as well as nonhepatic insults (namely extrahepatic sepsis) as a precipitating factors. Moreover, liver failure has not been defined with a view to select cases prospectively (though organ failure has been clearly defined). Main focus has been on recognizing organ failure by CLIF-SOFA score. Nonhepatic manifestation of liver failure gets more prominence in predicting outcome. Superiority of CLIF-SOFA score over other scores has also been shown in a few other studies.³⁸⁻⁴⁰

APASL definition is also based on a prospective follow-up of 1363 patients across Asia-Pacific region, but differs in many aspects from EASL-AASLD definition. It has insisted that precipitating cause should be 'hepatic insult' and does not accept extra-hepatic sepsis as a precipitating event. It is willing to accept variceal bleeding as a

precipitating event if it results in liver failure. Sepsis here is considered as a complication of ACLF, which results in immune paralysis. APASL definition is relatively easy to use as clearly outlines prospective selection criteria. These defining criteria, however, use an arbitrary cut off of serum bilirubin more than 5 mg/dL but has included all the WGO groups A, B and C which may have differing prognosis. The authors have argued about a hypothetical situation of a patient with Child's A cirrhosis who develops pneumonia, sepsis, and resultant renal failure. In this situation, EASL-AASLD definition will classify it as ACLF even when liver has not decompensated. They are also not happy with use of confusing terms as hepatic ACLF, extra-hepatic ACLF and infection related ACLF.⁶ A few Indian studies have noted that a simple organ failure score (the number of organ failures) may be easier for clinicians to use at the bedside and more convenient than the CLIF-SOFA score in predicting mortality in ACLF patients.^{38,41}

Clinical differences between these two concepts are also outlined in Figure 2. Lines E, F, and G represent the unique population seen in Asia-Pacific region. Here patients with relatively stable chronic liver disease (F3-4 fibrosis or Child's A cirrhosis) may develop superadded viral hepatitis or a flare of hepatitis B leading to development of ACLF. Many of these patients may be unaware that they have chronic liver disease and come to medical attention for the first time after decompensation. EASL-AASLD group basically sees patients with previously diagnosed alcoholic liver disease who deteriorate due to sepsis as represented by lines H, I and J. These patients possibly have decompensated cirrhosis (Child's stage B or C), who deteriorate in response to a precipitating event such as sepsis or bleeding (see legend to Figure 2).

Figure 2 Clinical course of acute liver failure (ALF) and acute on chronic liver failure (ACLF). Liver functions arbitrarily classified into normal, minor dysfunction, liver failure, multi-organ failure and death indicating increasing severity of liver failure. Line A depicts rapid deterioration in ALF and recovery. (Line B) A rare case who may recover from stage of multi-organ failure is also shown (line C). Line K represents progressive deterioration (decompensated cirrhosis or DC) of liver functions in natural course of cirrhosis. Line E depicts a cirrhosis patient in Child's A stage who develops ACLF, as in flare of Chronic Hepatitis B. Possible outcomes are shown by line G and F. Lines H depicts ACLF in a Child's B stage cirrhosis with its possible outcomes shown as lines I and J. A similar ACLF can also occur with a patient in Child's C Cirrhosis.

Whichever definition is used; one cannot deny the central role of infection in ACLF. It is the main precipitant of liver failure as per EASL-AASLD definition and the main consequence/complication of ACLF as per APASL definition. There have been attempts to classify the ACLF precipitated by infection as iACLF, which has high 30-day mortality.²⁸ Infections in cirrhosis have also been described as the fifth clinical stage with fourfold increase in mortality.⁴² Infections in this setting may be related to liver disease [e.g. spontaneous bacterial peritonitis (SBP)] or even unrelated to it (e.g. urinary tract infection, respiratory or skin/soft tissue infections) and both can lead to organ failures. Organ failures can be simply defined as hepatic encephalopathy (cerebral), AKI with rise in creatinine/need for RRT (Renal), changes in $\text{FiO}_2/\text{PaO}_2$ or need for ventilation (respiratory) and fall in MAP or need for vasopressor support (cardiovascular). NACSELD data showed 30-day mortality with 1, 2, 3 and 4 organ failures to be 13%, 26%, 64% and 72% respectively,²⁸ while EASL data also showed progressively higher 28-day and 90-day mortality with 1, 2 and 3 organ failure.³⁵

In terms of management, it is important to determine if infection is community acquired or healthcare associated and if it is 'first' infection or a 'second/subsequent' infection. It may also be important to understand the immune sequelae of infection as has been described by Hotchkiss et al.⁴³ Although both pro- and anti-inflammatory responses are activated; early in the course of sepsis, the proinflammatory response (represented by systemic immune response syndrome or SIRS) predominates. As sepsis becomes more advanced, the anti-inflammatory response becomes predominant (compensatory anti-immune response syndrome or CARS), and it is during this later phase that 'second/subsequent' infections and/or viral reactivation may occur. Early deaths during the pro-inflammatory response phase are due to cytokine storm-mediated events, whereas later deaths during the anti-inflammatory phase are due to failure to control pathogens. Thus usual signs of infection may not be apparent in latter stage but subtle clues that may direct one's attention to subsequent infections may be worsening hepatic encephalopathy, acute kidney injury and silent SBP in absence of usual leukocytosis response. A second infection independently decreases survival in iACLF²⁸ and is usually respiratory, urinary or *Clostridium difficile* infection related to healthcare. It is also eminently preventable. Judicious use of albumin can reduce mortality in SBP but possibly has no impact on other infections.⁴⁴

Whatever, the definition, prevention of infections, and its appropriate management can impact mortality. Judicious use of proton pump inhibitors, care of central line, urinary catheters and endotracheal tubes can go a long way in preventing second infections. Interestingly, a recent meta-analysis has shown that inappropriate selection of antibiotics can increase mortality.⁴⁵ Similarly, even a delay

of 3 h in starting antibiotics can impact survival. When Healthcare associated infections are suspected, a broader spectrum of antibiotics lowers treatment failure rates.⁴⁶

One situation where ACLF can be prospectively studied is the liver failure precipitated by iatrogenic interventions, such as transarterial chemoembolization or elective hepatic resection or non-hepatic surgery in known cases of cirrhosis. In all other situations, we analyze and quantify everything in retrospect except assessment of prognosis. In post-iatrogenic-intervention situation, patient characteristics are well known before liver failure, the precipitating event can be timed, the response to precipitating event can be monitored and organ failure course can also be closely followed. Studies so far have shown that Child-Pugh and MELD score prior to surgery are major determinants of post surgical outcome.^{47,48} In a Mayo clinic analysis, Independent predictors of 1-year postoperative mortality were MELD score, American Society of Anesthesiologists (ASA) class, and age. ASA class was best for predicting 7-day mortality, whereas MELD score was best for predicting 90-day mortality. Ninety-day mortality rate for patients with MELD scores of 8 or lower was 9.7%, for scores from 9 to 11 was 17.7%, for scores from 12 to 15 was 32.3%, and for scores higher than 15 was 55.8%.⁴⁸ Other factors that are known to determine the outcome are whether surgery has been performed as an emergency or as an elective procedure and nature/type of surgery. Preparing for surgery by optimizing treatment and planning a portal hypertension decompressing procedure can offset some of the disadvantage.⁴⁹ There may also be some intangibles which cannot be quantified, such as the experience and technical success of surgical and health care teams. However, the fact is that this setting offers a lot of hope in refining our knowledge about ACLF and possibly improving the definition in future.

It is amply clear that the definitions proposed by two main groups are seeing different types of patients from different geographical areas and hence it may not be unusual to have differing definitions. However, a recent study is significant as it seems to bring two definitions somewhat closer. On behalf of Indian Association for study of the liver (INASL) consortium for ACLF Research in the East or ICARE, Shalimar et al.³¹ have recently analyzed records of 1049 consecutive patients with ACLF satisfying APASL definition from 10 centers in India. They confirmed that mortality progressively increased with rising number of organ failures or OFs (12.3% with no OF and 83.3% with five OFs). On multivariate analysis by Cox proportional hazard model, the authors found elevated serum creatinine (hazard ratio: 1.176), advanced hepatic encephalopathy (hazard ratio: 2.698) and requirement of ventilator support (hazard ratio: 2.484) were independent predictors of mortality. Interestingly, this paper from East found that the mortality in the extra-hepatic insults in this cohort was 42.3%, similar to the overall mortality of the

cohort. This finding is similar to that found with EASL-AASLD definition which includes extra-hepatic insults as the acute precipitating events in the definition of ACLF. However, it is in contrast to the APASL definition of ACLF (validated predominantly in Indian patients) which includes only acute hepatic causes as precipitants of ACLF. ICARE results tend to suggest that extra-hepatic insults should be included as acute precipitants of ACLF. If accepted, it could bring two definitions a bit closer to each other.

The main question remains if and when we will find a common middle ground. One can only look at formulating an arbitrary logical definition covering all the shortcomings discussed above. For example, (a) one can classify pre-existing liver disease as per WGO classification, (b) precipitating event has been noted above, (c) time frame during which liver failure manifests as four weeks, (d) use either APASL definition forming the base line for defining liver failure or even use CLIF-SOFA definition of liver/coagulation failure and lastly (e) the quantification or prognostication of liver failure can be done using CLIF-SOFA score or a simpler number of organs failing. Dynamic criteria over first seven days may refine our prognostication efforts. It seems improbable that experts from these two groups will sit together and try to accommodate each other. In fact, such a meeting did take place sometime back, but the results were less than satisfactory.²⁹ Each group appears firm about what they have observed. Moreover, such a wider definition will be impossible to validate in the absence of worldwide database combining patients from all continents and countries. It appears that we destined to use two different definitions till that happens.

CONFLICTS OF INTEREST

The authors have none to declare.

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