

SUPPLEMENTARY MATERIAL**GLOBAL BURDEN OF DISEASE: ACUTE-ON-CHRONIC LIVER FAILURE, A
SYSTEMATIC REVIEW AND META-ANALYSIS**

Gabriel Mezzano, Adria Juanola, Andrés Cárdenas, Esteban Mezey, James P
Hamilton, Elisa Pose, Isabel Graupera, Pere Ginès, **Elsa Solà, Ruben Hernaez**

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Supplementary Table 1. Literature search criteria last updated on July 3rd, 2020.

Pubmed:

((acute-on-chronic liver failure) AND (mortality OR transplant) AND ("2013/03/01"[Date - Entrez] : "3000"[Date - Entrez])) NOT review

Embase:

'acute on chronic' AND ('liver' OR 'liver'/exp OR liver) AND ('failure' OR 'failure'/exp OR failure) AND ('mortality' OR 'mortality'/exp OR mortality) NOT ('review' OR 'review'/exp OR review) AND [embase]/lim AND [01-3-2013]/sd

Supplementary table 2. Diagnostic criteria of organ failure(s) (OFs) and acute-on-chronic liver failure (ACLF) according to the EASL CLIF definition (11).

Organ failure definition	
Liver (bilirubin, mg/dL)	≥12.0
Kidney (creatinine, mg/dL)	≥2.0 or renal replacement therapy
Brain (Hepatic Encephalopathy West Haven Criteria)	Grades 3–4
Coagulation (INR)	≥2.5
Circulation	Use of vasopressors
Lungs	PaO ₂ /FiO ₂ ≤200 or SpO ₂ /FiO ₂ ≤214 Or mechanical ventilation

ACLF definition and grades	
No ACLF	No organ failure; or single non-kidney organ failure (with serum creatinine <1.5mg/dL and no HE).
ACLF-1	Single kidney failure; or 1 non-kidney organ failure together with serum creatinine 1.5-.1.9mg/dL or grade 1-2 HE.
ACLF-2	Two organ failures.
ACLF-3	Three or more organ failures.

Supplementary Table 3. Newcastle-Ottawa Scale (NOS)

Author	ACLF cohort similar to original CANONIC	NON ACLF cohort similar to original CANONIC	Ascertainment of ACLF CANONIC	Use of CANONIC definition	Prevalent ACLF on inception	ACLF and non ACLF comparable?	Follow-up long enough 90 days at least	Adequacy of follow-up	Total
Europe									
Moreau et al 2013 (11)	1	1	1	1	1	1	1	1	8
McPhail et al 2016 (19)	1	1	1	1	0	0	1	1	6
Barosa et al 2017 (20)	1	1	1	1	0	1	1	1	7
Alexopoulou et al 2017 (21)	1	1	1	1	0	1	1	1	7
Huelin et al 2017 (22)	1	1	1	1	0	1	1	1	7
Antunes et al 2017 (23)	1	1	1	1	0	1	1	1	7
Piano et al 2017 (24)	1	1	1	1	1	1	1	0	7
Blasi et al 2019 (25)	0	0	1	1	0	1	1	1	5
Perdigoto et al 2019 (26)	1	1	1	1	0	1	1	1	7

Ferreira et al 2019 (27)	1	1	1	1	1	1	1	1	8
Mani et al 2019 (28)	1	1	1	1	1	1	1	1	8
Zaccherini et al 2019 (29)	1	0	1	1	1	0	1	1	6
Niewinski et al 2020 (30)	1	1	1	1	1	1	1	1	8
South America									
Silva et al 2015 (31)	1	1	1	1	0	1	1	1	7
Dominguez et al 2016 (32)	1	1	1	1	1	1	0	1	7
Picon et al 2017 (33)	1	1	1	1	0	1	1	1	7
Rosado et al 2019 (34)	1	1	1	1	1	1	0	1	7
Leao et al 2019 (35)	1	0	1	1	1	0	1	1	6
North America									
Hernaez et al 2019 (36)	1	1	1	1	1	1	1	1	8
Sundaram et al 2019 (37)	1	1	1	1	0	1	1	1	7

East Asia									
Shi et al 2015 (14)	1	1	1	1	0	1	1	1	7
Kim et al 2016 (38)	1	1	1	1	1	1	1	1	8
Shi et al 2017 (39)	1	1	1	1	0	1	1	1	7
Song et al 2018 (40)	1	1	1	1	0	1	1	1	7
South Asia									
Dhiman et al 2014 (41)	1	1	1	1	1	1	1	1	8
Amarapurkar et al 2015 (42)	1	0	1	1	1	0	0	1	4
Gupta et al 2017 (43)	1	1	1	1	0	1	1	1	7
Selva Rajoo et al 2017 (44)	1	1	1	1	1	1	1	1	8
Maipang et al 2019 (45)	1	0	1	1	1	0	1	1	6
Sirimongkol kasem et al 2019 (46)	1	1	1	1	1	1	1	1	8

Score conversion: 1:yes 0: No

Supplementary Table 4. Uniformity of EASL-CLIF definitions of ACLF

Author	ACLF definition	ACLF grade definition	Liver failure	Kidney failure	Brain failure	Coagulation failure	Circulatory failure	Respiratory failure
Europe								
Moreau et al 2013 (11)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12.0 mg/dL	Serum creatinine ≥ 2.0 mg/dL or the use of RRT	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥ 2.5 and/or a platelet count of 20 109/L or below	Use of dopamine, dobutamine, or terlipressin	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio < 200
McPhail et al 2016 (19)	EASL-CLIF criteria	NR	Serum bilirubin > 6 mg/dL	Serum creatinine ≥ 3.5 mg/dL	Grade III or IV hepatic encephalopathy, according to the West Haven classification	NR	NR	PaO ₂ /FiO ₂ ratio < 200 mmHg
Barosa et al 2017 (20)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12 mg/dl	Serum creatinine ≥ 2.0 mg/dl or the use of RRT	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥ 2.5	Use of vasopressors, with the exception of terlipressin in hepatorenal syndrome	SpO ₂ /FiO ₂ ≤ 214 or the need for mechanical ventilation
Alexopoulou et al 2017 (21)	EASL-CLIF	1,2,3 (see Suppl	Serum bilirubin	Serum creatinine \geq	Grade III or IV hepatic	INR ≥ 2.5 and/or a	The use of dopamine,	PaO ₂ /FiO ₂ ratio < 200 mmHg or an

	criteria	table 1)	≥ 12 mg/dl	2.0 mg/dl or the use of RRT	encephalopathy, according to the West Haven classification	platelet count of 20 109/L or below	dobutamine, or terlipressin	SpO ₂ /FiO ₂ ratio <200
Huelin et al 2017 (22)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Liver failure was defined by a serum bilirubin level of 12.0 mg/dL	Serum creatinine ≥ 2.0 mg/dl or the use of RRT	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥2.5 and/or a platelet count of 20 109/L or below	Use of dopamine, dobutamine, or terlipressin	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio <200
Antunes et al 2017 (23)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
Piano et al 2017 (24)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	NR	NR	NR	NR	NR
Blasi et al 2019 (25)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
Perdigoto et al 2019 (26)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12	Serum creatinine >2.0 mg/dL	Grade III or IV hepatic encephalopathy	NA	Use of vasopressors	NA
Ferreira et al 2019 (27)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥12.0	Serum creatinine ≥ 2.0 mg/dL or	Grade III or IV hepatic encephalopathy,	INR ≥2.5 and/or a platelet	Use of dopamine, dobutamine, or	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio

			mg/dL	the use of RRT	according to the West Haven classification	count of 20 109/L or below	terlipressin	<200
Mani et al 2019 (28)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12.0 mg/dL	Serum creatinine ≥ 2.0 mg/dL or the use of RRT	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥ 2.5 and/or a platelet count of 20 109/L or below	Use of dopamine, dobutamine, or terlipressin	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio <200
Zaccherini et al 2019 (29)	EASL-CLIF criteria	NR	Serum bilirubin ≥ 12.0 mg/dL	Serum creatinine ≥ 2.0 mg/dL or the use of RRT replacement therapy	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥ 2.5 and/or a platelet count of 20 109/L or below	Use of dopamine, dobutamine, or terlipressin	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio <200
Niewinski et al 2020 (30)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
South America								
Silva et al 2015 (31)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	NR	NR	NR	NR	NR
Dominguez et al 2016 (32)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12.0 mg/dL	Serum creatinine ≥ 2.0 mg/dL or the use of RRT replacement	Grade III or IV hepatic encephalopathy, according to the West Haven classification	INR ≥ 2.5 and/or a platelet count of 20 109/L or below	Use of dopamine, dobutamine, or terlipressin	PaO ₂ /FiO ₂ ratio < 200 mmHg or SpO ₂ /FiO ₂ ratio <200

				therapy				
Picon et al 2017 (33)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	NR	NR	NR	NR	NR
Rosado et al 2019 (34)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	NR	NR	NR	NR	NR
Leao et al 2019 (35)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	Serum creatinine > 2mg/dl	NR	NR	NR	NR
North America								
Hernaez et al 2019 (36)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥12.0 mg/dL	Serum creatinine > 2mg/dl or need of RRT (based on ICD-9 or CPT codes)	Hepatic encephalopathy present as diagnosis code during hospital stay	INR > 2.5	MAP < 60 mmHg and/or use of any doses of IV epinephrine, norepinephrine, dobutamine, dopamine, vasopressin	Need for mechanical ventilation (based on ICD-9 or CPT codes)
Sundaram et al 2019 (37)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin ≥ 12mg/dl	Insufficiency: creatinine 1.5–1.9 mg/dL Failure: creatinine >2.0 mg/dL or RRT	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5	Use of vasopressors	Use of mechanical ventilation

East Asia								
Shi et al 2015 (14)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin >12 mg/dL or 204 µmol/L	Serum creatinine > 2.0 mg/dL or 176 µmol/L	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5 or platelet count < 20.000	MAP < 70mmHg or need for vasopressors	PaO ₂ /FiO ₂ < 200 or SpO ₂ /FiO ₂ < 214 or need for mechanical ventilation
Kim et al 2016 (38)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
Shi et al 2017 (39)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
Song et al 2018 (40)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	NR	NR	NR	NR	NR	NR
South Asia								
Dhiman et al 2014 (41)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin > 12mg/dl	Serum creatinine > 2mg/dl or need of RRT	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5 or platelet count < 20.000	Use of vasopressors like dopamine, dobutamine, or terlipressin at any dose	PaO ₂ /FiO ₂ < 200 or SpO ₂ /FiO ₂ < 214
Amarapurkar et al 2015 (42)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin > 12mg/dl	Serum creatinine > 2mg/dl or need for RRT	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5 or platelet count < 20.000	Use of vasopressors	PaO ₂ /FiO ₂ < 200 or SpO ₂ /FiO ₂ < 214

Gupta et al 2017 (43)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin > 12mg/dl	Serum creatinine > 2mg/dl or need for RRT	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5 or platelet count < 20.000	MAP < 70mmHg or need for vasopressors	PaO ₂ /FiO ₂ < 200 or SpO ₂ /FiO ₂ < 214
Selva Rajoo et al 2017 (44)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR
Maipang et al 2019 (45)	EASL-CLIF criteria	1,2,3 (see Suppl table 1)	Serum bilirubin > 12mg/dl	Serum creatinine > 2mg/dl or need for RRT	Grade III and IV hepatic encephalopathy according to West Haven criteria	INR > 2.5 or platelet count < 20.000	MAP < 70mmHg or need for vasopressors	PaO ₂ /FiO ₂ < 200 or SpO ₂ /FiO ₂ < 214 or need for mechanical ventilation
Sirimongkolkasem et al 2019 (46)	EASL-CLIF criteria	NR	NR	NR	NR	NR	NR	NR

Supplementary Table 5. Loss of follow up

Author	Loss of follow up
Europe	
Moreau et al 2013 (11)	All at inception / less than 15%
McPhail et al 2016 (19)	All at inception / less than 15%
Barosa et al 2017 (20)	All at inception / less than 15%
Alexopoulou et al 2017 (21)	All at inception / less than 15%
Huelin et al 2017 (22)	All at inception / less than 15%
Antunes et al 2017 (23)	NA (not available)
Piano et al 2017 (24)	All at inception / less than 15%
Blasi et al 2019 (25)	All at inception / less than 15%
Perdigoto et al 2019 (26)	NA
Ferreira et al 2019 (27)	NA
Mani et al 2019 (28)	NA
Zaccherini et al 2019 (29)	NA
Niewinski et al 2020 (30)	NA
South America	
Silva et al 2015 (31)	NA
Dominguez et al 2016 (32)	NA
Picon et al 2017 (33)	All at inception / less than 15%
Rosado et al 2019 (34)	All at inception / less than 15%
Leao et al 2019 (35)	All at inception / less than 15%
North America	
Hernaez et al 2019 (36)	NA
Sundaram et al 2019 (37)	NA
East Asia	
Shi et al 2015 (14)	All at inception / less than 15%
Kim et al 2016 (38)	All at inception / less than 15%
Shi et al 2017 (39)	All at inception / less than 15%
Song et al 2018 (40)	All at inception / less than 15%
South Asia	

Dhiman et al 2014 (41)	All at inception / less than 15%
Amarapurkar et al 2015 (42)	All at inception / less than 15%
Gupta et al 2017 (43)	All at inception / less than 15%
Selva Rajoo et al 2017 (44)	NA
Maipang et al 2019 (45)	NA
Sirimongkolkasem et al 2019 (46)	NA

Supplementary table 6. Sensitivity analysis of prevalence (95%CI) data to address statistical heterogeneity

	ACLF	ACLF-1	ACLF-2	ACLF-3
Main findings	35 (33 – 38)	44 (41 – 47)	32 (28 – 35)	21 (17 – 24)
Prospective	40 (33 – 47)	45 (37 – 53)	33 (26 – 39)	20 (14 – 24)
Retrospective	30 (26 – 33)	44 (39 – 48)	30 (25 – 35)	22 (15 – 29)
NOS\geq5	35 (33 – 38)	44 (41 – 47)	32 (28 – 35)	21 (17 – 24)
UHC < 10th percentile	64 (49 – 79)	17 (8 – 26)	37 (26 – 49)	41 (30 – 53)

NOS, Newcastle-Ottawa Scale; UHC, Universal Health Coverage Index.

Blue shadow highlights major differences

Supplementary table 7. Sensitivity analysis of 90-day mortality data to address statistical heterogeneity.

	ACLF	ACLF-1	ACLF-2	ACLF-3
Main findings	58 (55 – 61)	32 (29 – 35)	55 (50 – 60)	80 (75 – 85)
Prospective	60 (54 – 66)	38 (32 – 43)	62 (52 – 72)	83 (79 – 88)
Retrospective	55 (50 – 59)	29 (26 – 32)	47 (42 – 52)	77 (71 – 83)
NOS\geq5	59 (55 – 62)	32 (29 – 35)	55 (50 – 60)	80 (75 – 85)
UHC < 10th percentile	73 (64 – 82)	27 (10 – 57)	79 (52 – 92)	--

NOS, Newcastle-Ottawa Scale; UHC, Universal Health Coverage Index.

Blue shadow highlights major differences

Supplementary Table 8. Differences in prevalence and mortality using meta-regression analysis and adjusting for different underlying etiologies and triggers. Summary of multiple-corrections corrected p-values highlighting significant vs. non statistically significant results (NO).

	Etiology Chronic Liver Disease		Triggers			
	Alcohol	Viral	Alcohol	Infection	GIB	Viral
Prevalence	Europe and South Asia (0.01)	Europe and South Asia (0.01)	Europe and South Asia (0.01)	Europe and South Asia (0.01)	Europe and South Asia (0.01)	South Asia (0.01)
Mortality	Europe and North America (0.01)	North-America(0.04)	NO	NO	NO	NO

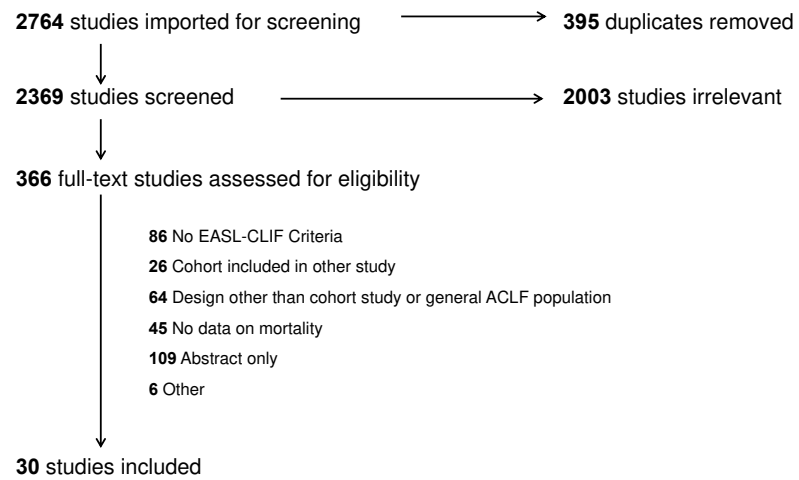
Supplementary Table 9. Egger's test p-values for small-study effects by Prevalence or 90-day Mortality analysis

	Prevalence	90-day mortality
ACLF	0.05	<0.01
Non AClF	--	0.76
ACLF 1	0.46	0.22
ACLF-2	0.82	<0.01
ACLF-3	0.74	<0.017

Supplementary Figure legends

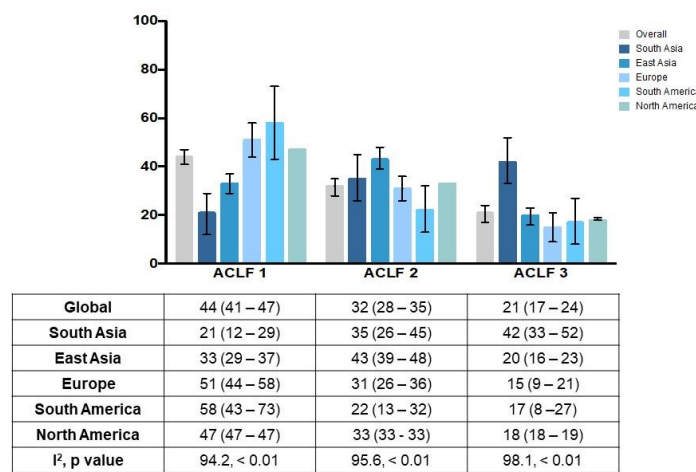
Supplementary figure 1. Flow chart of study selection.

Supplementary Figure 1.– Flow Chart



Supplementary figure 2. Prevalence of ACLF by grade.

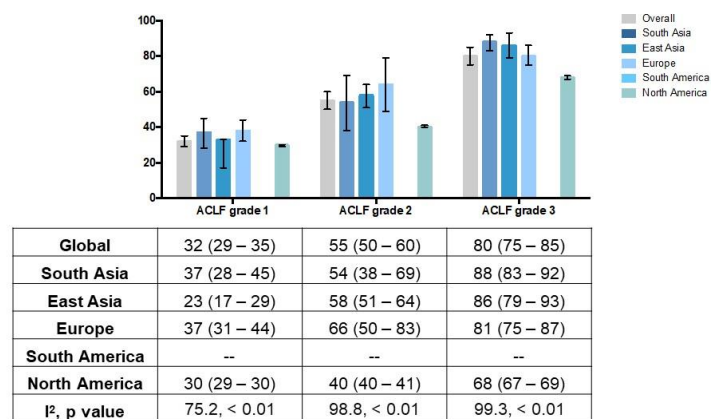
This figure shows the prevalence of ACLF categorized by grade according to the Canonic Study definition (ACLF-1, ACLF-2, ACLF-3). The figure includes data about the prevalence both worldwide and divided by regions (Europe, North and South America, East and South Asia). Numbers are percentages and 95% confidence interval (95%CI).

Supplementary Figure 2.- Prevalence of ACLF by regions and grade (% , 95% Confidence Interval)

Supplementary figure 3. 90-day mortality by grade.

This figure shows the 90-day mortality of patients with ACLF categorized by region (Europe, North and South America, East and South Asia) and grade according to the Canonic Study definition (ACLF-1, ACLF-2, ACLF-3). Numbers are percentages and 95% confidence interval (95%CI).

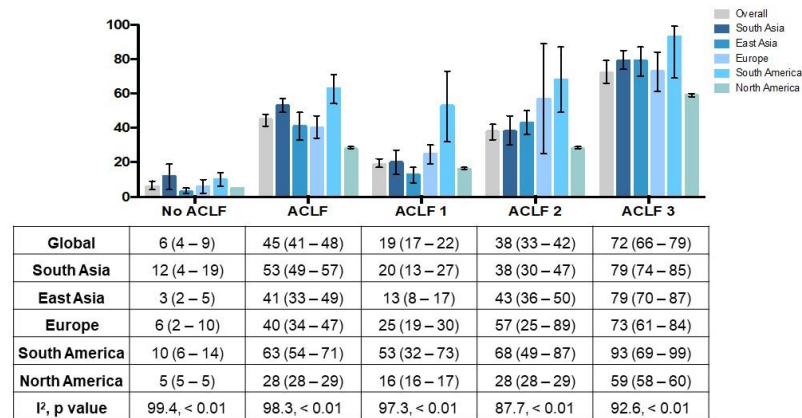
Supplementary Figure 3.- 90-day mortality by ACLF grade and regions (% , 95% Confidence Interval)



Supplementary figure 4. 28-day mortality.

This figure shows 28-day mortality of patients with ACLF worldwide and categorized by region (Europe, North and South America, East and South Asia) and grade according to the Canonic Study definition (ACLF-1, ACLF-2, ACLF-3). Numbers are percentages and 95% confidence interval (95%CI).

Supplementary Figure 4.- 28-day ACLF mortality by regions (% , 95% Confidence Interval)



Supplementary Figure 5. Funnel Plots in Prevalence and 90-Day mortality of ACLF presence and grades.

