Molecular Biology Testing for Non-Invasive Diagnosis of Allograft Rejection: LIVER

PICO 1: Can biomarkers be used to predict HCC recurrence?

Population: adult liver transplant candidates undergoing LT due to HCC related liver disease.
Intervention: use of biomarkers to predict HCC recurrence and thereby improve post-transplant monitoring
Comparators: use of classical models (up to seven Model, Milan criteria, Retreat Model)
Outcome: HCC recurrence, cost of post-transplant monitoring, HCC recurrence free survival and overall post-transplant survival

Author: M. Berenguer

STATEMENT: While preliminary studies suggest a role for molecular biomarkers measured in liquid biopsy (circulating tumor cells, in particular) in prediction of HCC recurrence, additional studies are needed before any recommendation can be issued regarding their application in clinical practice, either as predictive factors to select patients for liver transplantation or to guide post-transplant management.
Level of evidence: low (C)
Level of recommendation: weak for

REFERENCE	STUDY DESIGN	N	COHORT (CLINICAL TRIAL)	SETTING	TYPE OF PTS	BIOLOGICAL MARKER	TECHNIQUE	DISCOVERY VALIDATION	MAIN OUTCOME ASSESSED	MAIN RESULTS
Exosomal miRNA										
Nakano T, Chen I-H, Wang C-C, Chen P-J, Tseng H-P, Huang K-T, et al. Circulating exosomal miR-92b: Its role for cancer immunoediting and clinical value for prediction of posttransplant hepatocellular carcinoma recurrence. Am J Transpl (2019) 19:3250–62. doi: 10.1111/ajt.15490 53	Retro.	**LT: 121 HCC 93** CLD 28	No	PreLT Post-LT (1mo) Extra Mi LDLT	Adults All causes	**Exosomal miRNA** 92b	Microarray profiling qRT-PCR	D	Recurrence	- Post-LT, exosomal miR-92b level predicted early recurrence (AUC= 0.925, p < 0.001; sensitivity = 85.7%, specificity = 86.0%). - Circulating

										exosomes impact on HCC development partly through suppression of CD69 on NK cells my hepatoma-derived exosomal miR-92b
Sugimachi K, Matsumura T, Hirata H, Uchi R, Ueda M, Ueo H, et al. Identification of a bona fide microRNA biomarker in serum exosomes that predicts hepatocellular carcinoma recurrence after liver transplantation. Br J Cancer (2015) 112:532–8. doi: 10.1038/bjc.2014.621 54	Case control	**LT 65**	No	PreLT Extra Mi LDLT	Adults All causes	**Exosomal miRNA** 718, 1246	Microarray profiling qRT-PCR	V	Recurrence and RFS	- Exosomal miR-718 and miR-1246, were significantly downregulated and upregulated, respectively, in patients with recurrence compared to non-recurrent patients. - Low expression of miR-718 was associated with poorer histological differentiation (p = 0.026) and beyond Milan criteria status

										(p = 0.04). HOXB8 was identified as a potential target of miR-718 and its upregulation was associated with poor prognosis. - Exosomal miR-718 expression level was not associated with RFS (p = 0.13).
mRNA and MiRNA										
Cheung ST, Fan ST, Lee YT, Chow JP, Ng IO, Fong DY, et al. Albumin mRNA in plasma predicts post-transplant recurrence of patients with hepatocellular carcinoma. Transplantation (2008) 85:81–7. doi: 10.1097/ 01.tp.0000298003.88530.11 32	Retro	**LT82HCC72** CLD10HC10	No	PreLT Milan before 02 and USCF after 02	Adults All causes	**mRNA** Albumin	qRT-PCR	D	Recurrence OS RFS	Pre-LT, high level of albumin mRNA (>14.6) was a prognostic factor of: - Recurrence (HR, 5.9; 95% CI, 1.9–18.8; p = 0.002) - OS (HR, 4.6; 95% CI, 1.6–13.8; p = 0.006) - RFS (HR, 4.3; 95% CI, 1.6–11.8; p

										= 0.005). High plasma albumin mRNA level predicted 2-year HCC recurrence with sensitivity and specificity of 73% and 70%, respectively
Oya H, Sato Y, Yamamoto S, Nakatsuka H, Kobayashi T, Hara Y, et al. Comparison between human-telomerase reverse transcriptase mRNA and alpha- fetoprotein mRNA as a predictive value for recurrence of hepatocellular carcinoma in living donor liver transplantation. Transplant Proc (2006) 38:3636–9. doi: 10.1016/j.transproceed.2006.10.172 33	Retro	14	No	PreLT Post LT Milan and extra Mi LDLT	Adults All causes	**mRNA** h-TERT AFP	RT-PCR	D	RFS	Pre-LT h-TERT mRNA level was associated with RFS (p = 0.005) but not AFP mRNA (p = 0.23). RFS □ No significant difference between those who met Milan and those who did nott; and no difference among positive vs. negative AFP mRNA
Marubashi S, Dono K, Nagano H, Sugita Y, Asaoka T, Hama N, et al. Detection of AFP mRNA-expressing cells in the	Prosp. Case	**LT 48 HC**	No	Pre, intra, post	Adults	**mRNA** AFP	qRT-PCR		Recurrence	Pre-LT AFP mRNA was a

peripheral blood for prediction of HCC recurrence after living donor liver transplantation. Transpl Int (2007) 20:576– 82. doi: 10.1111/j.1432-2277.2007.00480.x 34	control	**C 32** ESLD 16 LDC 48		Milan and extra Mi LDLT	All causes					prognostic factor of recurrence (HR, 10.8; 95% CI, 1.53-76.9; p= 0.017)
Wang Y, Shen Z, Zhu Z, Han R, Huai M. Clinical values of AFP, GPC3 mRNA in peripheral blood for prediction of hepatocellular carcinoma recurrence following OLT: AFP, GPC3 mRNA for prediction of HCC. Hepat Mon (2011) 11:195–9. 35	Retro Case Control	**LT 49 HCC 29** CLD 20 HC 20	No	Pre, intra, post Milan and extra Mi	Adults HBV and HCV	**mRNA** AFP GPC3	RT-PCR	D	Early recurrence (12mo of follow-up)	- Pre-LT, AFP mRNA level was a prognostic factor of recurrence (RR, 2.91; 95% CI, 1.09–7.76; p = 0.033). - Post-LT, AFP mRNA level was not a prognostic factor of recurrence (RR, 2.62; 95% CI, 0.93–7.41; p = 0.07). - GPC3 mRNA level was not associated with recurrence.
Hwang HS, Yoo JE, Han DH, Choi JS, Lee JG, Joo DJ, et al. Circulating cancer stem cells expressing EpCAM/CD90 in hepatocellular carcinoma: A pilot study for predicting tumor	Prosp. Cohort	25	No	PreLT Post LT (POD d1/7)	Adults All causes	**mRNA** K19 EpCAM CD90 SNAIL TWIST	qRT-PCR	D	Recurrence DFS	- EpCAM and CD90 mRNA levels

recurrence after living donor liver transplantation. Gut Liver (2022) 16(3):443–455. doi: 10.5009/gnl210162 26				Milan and down staged LDLT	HBV 22, 1 HCV, 2 non B non C hepatitis					correlated with the detection rate of EpCAM^{+} and CD90^{+} CTCs but showed no prognostic value. EpCAM+/CD90+ CTC can be used preoperatively and 1 day after LDLT as markers iin LT selection and postLDLT management. - mRNA levels of K19, SNAIL and TWIST were not associated with recurrence.
HuangA,GuoD-Z,WangY-P,YangG-H,SunQ-M,ZhangX,etal.Plasma MicroRNA panel predicts early tumor recurrence in patients with hepatocellular carcinoma after liver transplantation. J Cancer (2021) 12:7190–200. doi: 10.7150/ jca.59612 36	Retro	**LT213 HCC193** ESLD 20	No	PreLT Post LT (POD 1-6/7, 14) Milan and extra Mi	Adults All causes	**miRNA** miR 122, 192, 21, 223,26[a], 27[a], 801	qRT-PCR	V	Early recurrence	- Positive miR panel status in the late phase (7–14 days) was a prognostic factor of recurrence (HR, 4.90;

										95% CI, 2.20–10.95; p < 0.001). - mi-R panel was an earlier predictor of recurrence than AFP and DCP. In addition, it preceded evidence of recurrence on imaging with a median delay of 2.4 months (0.5-10.0mo).
Ng KT-P, Lo CM, Wong N, Li CX, Qi X, Liu XB, et al. Early-phase circulating miRNAs predict tumor recurrence and survival of hepatocellular carcinoma patients after liver transplantation. Oncotarget (2016) 7:19824–39. doi: 10.18632/oncotarget.7627 37	Retro	**LT62HC12**	No	PreLT Post LT (2h, POD 1 and 1w) Milan and extra Mi	Adults All causes	**miRNA** miR 148[a], 1246, 1290, Let7c, 21,23b,27b,122,125b, 151-5p, 192,195,199a-3p, 215		V	DFS and OS Recurrence	miR-148a (p=0.03) and miR (p=0.009) were significant predictors of HCC recurrence In the early phase (2-h after portal vein reperfusion), upregulation of miR-1246 was a prognostic predictor of both

										DFS (HR, 10.12; 95% CI, 1.45–70.47; p = 0.020) and OS (HR, 10.24; 95% CI, 1.39–75.67; p = 0.023).
Circulating T CELLS										
Xue F, Shi S, Zhang Z, Xu C, Zheng J, Qin T, et al. Application of a novel liquid biopsy in patients with hepatocellular carcinoma undergoing liver transplantation. Oncol Lett (2018) 15:5481–8. doi: 10.3892/ol.2018.8019 20	Retro Case control	**LT 30 HC 10**	No	PreLT Post LT (3mo) Milan and extra Mi	Adults All causes (23 HBV, 3 HCV, 4 other)	**CTC** CEP8, CK+, DAPI+, CD45-	iFISH CellSearch	V	Recurrence and recurrence free survival	- Comparison of detection performance of iFISH® vs. CellSearch®: performance of iFISH® was higher than CellSearch® (sensitivity 70% vs. 26.7%; p < 0.01). Threshold >5/7.5 ml - Pre-LT iFISH® CTC count predicted recurrence on univariable analysis (HR, 5.14; 95% CI, 1.53-17.31; p

										= 0.008).
Wang P-X, Xu Y, Sun Y-F, Cheng J-W, Zhou K-Q, Wu S-Y, et al. Detection of circulating tumour cells enables early recurrence prediction in hepatocellular carcinoma patients undergoing liver transplantation. Liver Int (2021) 41:562–73. doi: 10.1111/liv.14734 22	Retro	**LT193**	No	PreLT Post LT (1mo and months)	Adults	**CTC** EpCAM+, Pan-CK+, CK19+, DAPI+, CD45-	ChimeraXil20 Single-cell whole genome sequencing		Recurrence	- Pre-LT CTC count showed low predictive value for recurrence - Post-LT CTC count was a prognostic factor for recurrence (HR, 2.67; 95% CI, 1.51–4.74; p = 0.001).
Chen Z, Lin X, Chen C, Chen Y, Zhao Q, Wu L, et al. Analysis of preoperative circulating tumor cells for recurrence in patients with hepatocellular carcinoma after liver transplantation. Ann Transl Med (2020) 8:1067. doi: 10.21037/atm-20-2751 23	Retro	**LT50**	No	PreLT Milan and extra Mi	Adults All causes (38 HBV)	**CTC** CEP8 DAPI+ CD45-	Negative enrichment and imFISH	D	Early recurrence DFS OS	Pre-LT CTC count was a prognostic factor for recurrence (RR, 5.41; 95% CI, 1.13–25.87; p = 0.034). Threshold >1/3.2 ml 1-year DFS rate of CTC-neg and CTC -positive patients were 91.7 and 61.5% respecti

										vely (p.=0.02). The 1-year OS of CTC-positive and CTC-neg was 88.5% and 91.7%, respectively (p=0..751)
WangS,ZhengY,LiuJ,HuoF,ZhouJ.Analysisofcirculatingtumorcellsin patients with hepatocellular carcinoma recurrence following liver transplantation. J Investig Med (2018) 66:1–6. doi: 10.1136/jim-2017-000655 24	Prosp Cohort	**LT 47**	No	PreLT Post LT (1 mo and months) Milan and Extra Mi	Adults Only HBV	**CTC** EpCAM+, CK8+, CK18+, CK-19+, DAPI+, CD45-, Vimentin+, Twist+	CanPatrol RNA-ISH	D	Recurrence	- Three different subtypes of CTCs were identified: epithelial, interstitial and mixed. - Post-LT, changes in the proportion of CTCs subtypes were observed (increased epithelial and interstitial CTC levels). - CTC count and subtypes were not predictive of recurrence (p > 0.05).
Xie Y-L, Yang Z, Feng X, Yang Q, Ye L-S, Li X-B, et al. Association of phenotypic transformation of circulating tumor cells and early recurrence in patients with	Retro	**LT 56**	No	PreLT Post-LT (POD 7-10)	Adults All causes	**CTC** EpCAM+, CK8+, CK18+, CK19+,	CanPatrol RNA-ISH	D	Recurrence	- Three different subtypes of CTCs

hepatocellular carcinoma following liver transplantation. Asian J Surg (2022) 45:435–40. doi: 10.1016/j.asjsur.2021.07.058 25				Milan and extra Mi	(52 HBs Ag+)	Vimentin+ , twist+				were identified: epithelial, interstitial and mixed. Interstitial CTCs showed particular interest. - A perioperative increasing proportion of interstitial CTC was a prognostic factor of recurrence (HR, 6.17; 95% CI, 1.89–20.18; p = 0.003).
Hwang HS, Yoo JE, Han DH, Choi JS, Lee JG, Joo DJ, et al. Circulating cancer stem cells expressing EpCAM/CD90 in hepatocellular carcinoma: A pilot study for predicting tumor recurrence after living donor liver transplantation. Gut Liver (2022) 16(3):443–455. doi: 10.5009/gnl210162 26	Pro sp. Co hort	**LT 25**	No	PreL T Post LT (POD 1/7) Milan and extra mi LDLT	Adu lts All cau ses HB V 22, 1 HC V, 2 non B non C hep atiti s	**CTC** EpCAM+ CD90+ CD45-	Fluor escen c Activa ted cell sortin g	D	Recu rrenc e DFS	- Three different subtypes of CTCs were identified: EpCAM^{+} (epithelial), CD90^{+} (mesenchymal) and EpCAM^{+}/CD90^{+} (mixed). - Pre-LT, EpCAM^{+} CTC count was associa

										ted with lower DFS (p = 0.025). - Detection of EpCAM^{+}/CD90^{+} CTCs on POD 1 was a prognostic factor of recurrence (HR, 26.88; 95% CI, 1.86–387.51; p = 0.016).

PICO 2: Can biomarkers be used to diagnose recurrent liver diseases after liver transplantation?

Population: Adult liver transplantation patients with and without elevated liver enzymes

Intervention: Use of biomarkers to diagnose recurrent disease
Comparators: Diagnosis of recurrent disease based on liver biopsy +/- imaging data
Outcome: Recurrent disease in the graft (NASH, ASH, AIH, PBC)
Author: E. de Martin/ Co-author: Alina Lutu

STATEMENT: The use of biomarker assays can't reliably predict/diagnose disease recurrence after liver transplantation.

Level of evidence: low (C)
Level of recommendation: strong

QUALITY ASSESSMENT							QUALITY	IMPORTANCE	RECOMMENDATION
Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	QUALITY	IMPORTANCE	RECOMMENDATION
AIH Recurrence	2	retrospective studies	serious	serious	not serious	serious	very low	critical	strong for

PBC Recurrence	4	retrospective studies	serious	serious	serious	serious	very low	critical	strong for
PSC Recurrence	2	retrospective studies	serious	serious	serious	serious	very low	critical	strong for
NASH Recurrence	2	retrospective studies	serious	serious	serious	serious	very low	critical	strong for

1=author/journal/date	**Study type**	**No. of patients**	**Main outcomes assessed and results**
AIH			
Gonzalez, Liver Transplantation, 2001	Observational prospective	**41**	Frequency, risk factors, consequence of recurrence. Recurrence in 7 (17%) patients. Recurrent autoimmune hepatitis more commonly had **HLA-DR3 or HLA-DR4**
Duclos-Vallée, Gut 2003	Observational non comparative retrospective	**17**	Long-term outcome (10-year) Recurrence in 7 (41%) patients. **HLA DR3**
PBC			
Sanchez, Transplantation, 2003	Observational comparative retrospective	**156**	Recurrence Recurrence 17 (10.9%). **Donor alleles A1, B57, B58, DR44, DR57, and DR58** were found at an increased frequency. The only **recipient** allele of significance was **B48**. Not any statistically significant difference in mis- matches.
Guy, Liver Transplantation, 2005	Observation comparative retrospective	**48**	Risk factors for PBC recurrence. Recurrence in 27 (56%) patients. Increased mismatch of **donor DR3 and recipient DR4** in patients with recurrent PBC (p<0.055)
Morioka, Liver Transplantation, 2007	Observation comparative retrospective	**50**	Patient survival and PBC recurrence in LDLT. Recurrence 9. a **higher n**umber of **HLA-A, -B, and -DR mismatches** between donor and recipient the presence of persistent ascites before LDLT, (donor age > 50 years) > survival. **Lower number of HLA mismatches** between donor and recipient, and a lower average trough level of tacrolimus within 1 year after LDLT > recurrence.
Carbone, AJT 2013	Observation comparative retrospective	**248**	Risk loci for PBC in the native liver might influence the risk of PBC recurring Recurrence 105 (42.3%) **SNPs rs62270414**
PSC **The PSC group in which I am also involved had a specific question regarding CSP recurrence. Here I selected paper that mention biomarkers.**			
Alexander, Liver Transplantation 2008	Observational comparative retrospective	**69**	Risk factors recurrence Recurrence 7 (10%). Presence of **HLA-DRB1*08 in recipient** (+ Rejection episodes and steroid-resistant rejection)
Bajer, *World J Gastroenterol* 2018	Observational non comparative retrospective	**47**	Risk factors recurrence Recurrence 21. **HLA-DRB1*07 in the donor**
NASH			
Finkenstedt, Clin Gastro and Hepatol 2013	Observational non comparative retrospective	**237 recipients 95 with macrovesicular steatosis**	Association of donor and recipient risk alleles Recipient who carried **rs738409-GG** in PNPLA3 had a 13.7-fold higher risk of graft steatosis

Mowry, Transpl Direct 2021	Observational non comparative retrospective	**37**	NAFLD vs NASH Identification of 14 circulating metabolites characterizing NAFLD (vs normal liver) Identification of 16 circulating metabolites characterizing NASH (vs NAFLD)

PICO 3: Can biomarkers be used to safely wean IS (minimization and eventually full withdrawal)?

Population: Liver transplant recipients receiving maintenance immunosuppression Intervention: Use of biomarkers to guide IS minimization and withdrawal
Comparators: IS minimization and withdrawal based on classical clinical approach (risk factors associated with rejection, time from LT, trough levels)
Outcome: weaning IS without rejection, time to minimal / no immunosuppression, adverse events associated with IS (Diabetes, AHT, CVD, de novo cancer), subclinical graft injury
acute rejection

Author: V. Mas/Co-Author: H. Zubair

STATEMENT: 1. Moderate evidence suggests that DSA can be a marker for monitoring ISW.
2. Moderate evidence supports that blood-borne molecular markers such as donor-derived cell-free DNA and transcriptomic profile have the potential to be a marker of ISW and acute injury
3. There are multiple clinical trials that are recruiting or just completed recruiting patients for clinical biomarker development, such as NCT01672164, NCT04793360, NCT02533180, and NCT02498977 (Clinicaltrials.gov), during the preparation of this consensus recommendation. These clinical trials focus on molecular and non-invasive biomarkers of ISW and/or acute injury. It is expected completion of these studies will provide additional validation of the non-invasive biomarkers in the liver transplant setting supporting their utility in the coming years.
4. Based on the evidence from the existing preliminary data the role of molecular and non-invasive biomarkers seems feasible. However, we recommend the generation of additional data from larger multi-centre studies, with mixed gender and race populations, which include a strong criterion for analytical evaluation followed by a separate validation cohort for markers identified. Additionally, these studies should include longitudinal cohorts to follow the progression of Tolerance induction or injury episode to clearly delineate the prognostic properties of the biomarkers.
Level of evidence: low (C)
Level of recommendation: weak for

QUALITY ASSESSMENT								NO. OF PATIENTS			QUALITY	IMPORTANCE	RECOMMENDATION
Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	treatment x	standard care	.	QUALITY	IMPORTANCE	RECOMMENDATION

Index Test 1: dnDSA generation increases during acute injury while ISW	1	RCT	serious	not serious	not serious	not serious		31	9	moderate	important but not critical	weak for
Index Test 2: Increase in portal vein infiltrates with elapsed time post ISW	1	retrospective studies	serious	not serious	serious	not serious		38	0	very low	not critical	weak for
Index Test 3: Ex vivo cytokine production by cultured CD4+ cells increases upon ISW in tolerant patients	1	cohort studies	serious	serious	not serious	not serious		24	0	low	not critical	weak for
Index Test 4: Heightened intrahepatic Interferon Stimulated Gene expression and immunoregulatory transcript levels, and circulating immune-exhausted HCV-specific CD8+ T cells is higher pre-ISW in HCV+ LT recipients	1	cohort studies	serious	not serious	not serious	not serious		32	0	low	not critical	weak for
Index Test 5: High intrahepatic iron-homeostasis associated gene expression predicts development of tolerance upon ISW	1	cohort studies	not serious	not serious	not serious	not serious		144	0	low	important but not critical	weak for
Index Test 6: Serum hepcidin and ferritin is higher in patients with successful tolerance induction upon Isw	1	cohort studies	not serious	not serious	not serious	not serious		80	0	low	important but not critical	weak for
Index Test 7: T-cell production of IFN-γ is higher in patients with success tolerance induction upon ISW	1	cohort studies	not serious	not serious	not serious	not serious		24	0	low	important but not critical	weak for
Index Test 8: Intrahepatic 11-gene marker for probable	1	cohort studies	not serious	not serious	not serious	not serious		341	0	low	not critical	weak for

TCMR identifies acute injury upon ISW												
Index Test 9: Combination of ALT with DSAs identifies acute injury upon ISW	1	cohort studies	not serious	not serious	not serious	not serious		157		low	important but not critical	weak for
Index Test 10: Combination of ALT with antibodies against class II HLA	1	cohort studies	not serious	serious	not serious	not serious		185		low	important but not critical	weak for
Index Test 11: serum miRNA profiles of miRNAs (miR-483-3p and miR-885-5p) identify injury upon ISW	1	cohort studies	not serious	not serious	not serious	not serious		130		moderate	important but not critical	weak for
Index Test 12: Serum galectin-1 expression is lower in patients with acute rejection in liver transplant recipients	1	cohort studies	serious	not serious	not serious	not serious		45		low	not critical	weak for
Index Text 13: Increase in ddcfDNA indicates acute injury in liver transplant recipients	3	cohort studies	not serious	serious	not serious	not serious		404		low	important but not critical	weak for
Index Test 14: serum Diagnostic signature of miR-122 + miR 210 increases upon acute rejection	1	cohort studies	serious	not serious	not serious	not serious		30	0	moderate	not critical	weak for
Index Test 15: Gene expression profile identifies acute rejection cases in liver transplant	2	cohort studies	not serious	not serious	not serious	not serious		121	257	low	important but not critical	strong for
Index Test 16: plasma signature of miR-181a-5p increases upon acute rejection	1	cohort studies	not serious	not serious	not serious	not serious		145		low	not critical	weak for
Index Test 17: hepatocyte-specific methylated PTK2B as marker of dd-cf-DNA for acute rejection	1	cohort studies	serious	not serious	not serious	not serious		51		low	not critical	weak for

PICO 4: Can biomarkers be used to predict chronic kidney disease (CKD) in liver transplant recipients?

Population: Adult liver transplant recipients receiving maintenance immunosuppression
Intervention: Use of biomarkers to predict future development of CKD and progression to end stage renal disease (ESRD)
Comparator: CKD prediction based on classical clinical approach (risk factors associated with CKD such as diabetes, hypertension, age, pre-LT kidney function, trough levels of calcineurin inhibitors, etc)
Outcome: Development of CKD stage III (<60 ml/min eGFR)
Progression through different stages of CKD (I to V)
Development of ESRD (CKD stage V), need for hemodialysis, need for kidney transplantation
Patient/graft survival in relation to CKD stage

Author: J. Levitsky/Co-author: N. Wahid

STATEMENT: We suggest that biomarker assays may be able to help predict chronic kidney disease after liver transplantation.
Level of evidence: low (C)
Level of recommendation: weak for

Paper	notes	GRADE
Levitsky 2020	PRESERVE Outcome- GFR at year 1 and 5; CKD=>10% decline in GFR over 12 months Multicenter discovery (CTOT14, n=60), single center validation (BUMC, n=50) Predictive model using b2mg, cd40 antigen, hcv infection AUC 0.814 in discovery and 0.801 in validation	Moderate (B)
Cullaro 2018	Outcome- post-LT CKD (GFR<60 for 3 months) Single center; n=92; median follow-up 4.6-5.1 yrs; Urinary neutrophil gelatinase-associated lipocalin (uNGAL) at 24 hours, 24 hour post-LT renal fxn, initial calcineurin inhibitor, and age were independent predictors of CKD AUC for uNGAL24h for CKD at 4yrs was 0.65; when all the above variables combined in model- AUC 0.84 at 4 years post-tx	Low (C)

	Limitations- low sample size, single center; no validation cohort;	
Levitsky 2011	N=342 patients (single center) with baseline GFR>60 and are now >3 yrs post-LT Three groups: GFR >90, 60-90, <60 Age, cyclosporine use, and pre-LT GFR independently associated with new onset CKD N=64 in proteomic evaluations; (test- 22, validate-42), 10 proteins associated with new CKD AUC 0.78	Low (C)
Milongo 2015	N= 80, Assessed thousands of peptides (in the urinary peptidome), none associated with CKD at 6 mo (GFR<60) Viral hepatitis sole independent predictor for CKD	Very low (D)

CLINICAL ONLY MODELS FOR PREDICTING CKD

Guo 2022	Outcome- CKD at 1, 3, 5 years post OLT (GFR<60 for >3 mo) Retrospective, 399 patients Training, validation set Multivariate cox regression Factors- age at surgery (HR 1.0), female sex (HR 2.9), postop htn (HR 1.7), pre-op eGFR (HR 1.0), uric acid at 3 months (HR 1.0), hgb at 3 months (HR 0.97), cyclosporin A at 3 mo (HR 1.00) C-indices 0.75 and 0.8 0 (training and validation set) Advantages- -practical (commonly tested labs) -tranining and validation set Disadvantages -retrospective, single center; small sample size	Moderate (B)
Giusto 2013	Prospective, n=179, median 63 mo follow-up Validation sample- 149 patients from single center CKD=GFR<60 in two samples 3 months apart GFR at LT was only independent risk factor pre-tx; arterial htn (HR 1.83), severe infxn (HR 2.15) and estimated GFR (HR 0.89) independent risk factors post-tx	Low (C)
Israni 2013	Retrospective, SRTR database merged with US Renal Data System; prediction model limited to MELD era (n=36k)	Moderate (B)

	Early prediction model- c statistic 0.78 (6 mo) Late onset ESRD model- c-statistic 0.74, (6 mo and 5 mo)	
Lin 2012	CKD at 5 yrs post-LT N=77 patients, >2 yr follow-up Multivariate analysis- development of CKD associated with post-tx 4 week Cr Non-randomized; intension to treat (converted from CNI to sirolimus) Cr 1.05, NPV 94.5%; PPV 31.8%	Very low (D)
Burra 2009	Pre-tx factors association with renal failure at 1 yr and 5 yrs post-tx (GFR<60) N=1948 patients in multinational observational study in tx (MOST) registry Multivariate analysis- HCV status, pre-LT Cr and gender predictors of 1 year GFR (R-squared=0.12) but only 1 yr GFR was predictor of 5 yr GFR	Low (C)
Velidedeoglu 2004	N=181, single center; erxcluded patients who died; mean 2.7 yr followup Renal dysfunction=Cr>2 (acute or chronic) Post-tx dm (OR 5.7), early post-op ARD (OR 10.2) significantly associated with chronic renal dz in logistic regression	Low (C)
Pawarode 2003	N=172 , CKD= decrease in GFR>30 for at least 6 months or severe renal failure (GFR<30 for >6 mo) Cr >1.2 pre-tx, GFR<70 at baseline were independent predictors of permanent renal dysfunction (HR 3.2 and 12.7, respectively) ; severe renal failure- independent risk factors- DM, CAD (HR 8.0 and 15.7)	Moderate (B)