Association of preoperative parameters with postoperative mortality and long-term survival after liver transplantation

Dionisios Vrochides, MD, PhD*
Mazzen Hassanain, MD, PhD*†
Jeffrey Barkun, MD*
Jean Tchervenkov, MD*
Steven Paraskevas, MD, PhD*
Prosanto Chaudhury, MD*
Marcelo Cantarovich, MD*
Marc Deschenes, MD*
Phil Wong, MD*
Peter Ghali, MD*
Gabriel Chan, MD*
Peter Metrakos, MD*†

From the *Department of Surgery and the *Multi-Organ Transplant Program, McGill University, Montréal, Que., and the †Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia

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Correspondence to:
Dr. D. Vrochides
Royal Victoria Hospital
687 Pine Ave. W, S10.26
Montréal QC H3A 1A1
vrochides@yahoo.com

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Background: The ability of Child–Turcotte–Pugh (CTP) or Model for End-Stage Liver Disease (MELD) scores to predict recipient survival after liver transplantation is controversial. This analysis aims to identify preoperative parameters that might be associated with early postoperative mortality and long-term survival after liver transplantation.

Methods: We studied a total of 15 parameters, using both univariate and multivariate models, among adults who underwent primary liver transplantation.

Results: A total of 458 primary adult liver transplants were performed. Fifty-seven (12.44%) patients died during the first 3 postoperative months and composed the early mortality group. The remaining 401 patients composed the long-term patient survival group. The parameters that were identified through univariate analysis to be associated with early postoperative mortality were CTP score, MELD score, bilirubin, creatinine, international normalized ratio and warm ischemia time (WIT). In all multivariate models, WIT retained its statistical significance. The 10-year long-term survival was 65%. The parameters that were identified to be independent predictors of long-term survival were the recipient's sex (improved survival in women, $p = 0.005$), diagnosis of hepatocellular cancer ($p = 0.015$) and recipient's age ($p = 0.024$).

Conclusion: Either CTP or MELD score, in conjunction with WIT, might have a role in predicting early postoperative mortality after liver transplantation, whereas the recipient's sex and the absence of hepatocellular cancer are associated with improved long-term survival.

Contexte : La capacité des scores de Child–Turcotte–Pugh (CTP) ou du modèle de maladies du foie au stade ultime (MELD) de prédire la survie des receveurs après une transplantation hépatique suscite la controverse. Cette analyse vise à déterminer les paramètres préopératoires qu'il serait possible d'associer à la mortalité postopératoire précoce et à la survie à long terme après une transplantation hépatique.

Méthodes : Nous avons étudié au total 15 paramètres en utilisant des analyses unidimensionnelles et à variables multidimensionnelles chez les adultes qui ont subi une transplantation primaire du foie.

Résultats : Au total, 458 transplantations hépatiques primaires ont été pratiquées chez des adultes. Cinquante-sept (12,44 %) des patients sont morts au cours des 3 mois qui ont suivi l'intervention et ont constitué le groupe de la mortalité précoce. Les 401 autres patients ont constitué le groupe de la survie à long terme. Les paramètres que l'analyse unidimensionnelle a révélés associés à la mortalité postopératoire précoce étaient le score de CTP, le score du MELD, la bilirubine, la créatinine, le rapport international normalisé et la période d'ischémie chaude (PIC). Dans tous les modèles multidimensionnels, la PIC a gardé son importance statistique. La survie à long terme à 10 ans s'est établie à 65 %. Les paramètres considérés comme des prédicteurs indépendants de la survie à long terme étaient le sexe du receveur (meilleure survie chez les femmes, $p = 0{,}005$), le diagnostic de cancer hépatocellulaire ($p = 0{,}015$) et l'âge du receveur ($p = 0{,}024$).

Conclusion : Les scores de CTP ou du MELD conjugués à la PIC pourraient avoir un rôle à jouer dans la prédiction de la mortalité postopératoire précoce après une transplantation hépatique, tandis qu'on établit un lien entre le sexe du receveur et l'absence de cancer hépatocellulaire et une meilleure survie à long terme.

The Model for End-Stage Liver Disease (MELD) score is now used for allocation in liver transplantation waiting lists, replacing the Child–Turcotte–Pugh (CTP) score. The MELD score is primarily a "justice"

system (i.e., organs from deceased donors are allocated to the sickest patients first).[1] However, implementation of the MELD score has raised the issue of utility of the donated liver grafts.[2] According to the "utility" concept (i.e., organs are allocated preferentially to the lowest-risk candidates), an ideal liver allocation model should not only identify the patient with the highest probability of dying on the waiting list, but also predict early postoperative mortality and long-term survival. Early postoperative mortality usually is associated with technical failures, high-risk recipients and poor-quality grafts. On the other hand, long-term survival is compromised by recurrence of primary disease, opportunistic infections and development of cancer.[3] Because of this difference in causative factors, prediction of early and late mortality after liver transplantation might be associated with different preoperative parameters.

Most of the scores assessing the severity of cirrhosis, including CTP and MELD scores, have also been used to predict early mortality after liver transplantation,[4] but usually without success. For example, the MELD score was unable to predict early (90-d) postoperative mortality in almost all of the relevant studies.[5–7] To increase their accuracy, the most recent models for the prediction of early postoperative mortality have included the MELD score and many other variables, such as serum sodium,[8] donor quality[9] or serum cholinesterase.[10]

Prediction of long-term survival alone after liver transplantation is less well studied. Most of the relevant studies either utilize the MELD score or derive from a hepatitis C virus (HCV) patient population. Some of the former studies suggest that the MELD score can accurately predict late posttransplant mortality,[11] whereas some others do not.[12] On the other hand, analyses based on HCV population incorporate many other variables, such as donor's sex and recipient's age, in the predictive model.[13]

This study aims to identify preoperative parameters that might be associated with early postoperative mortality and long-term survival after liver transplantation.

Methods

We performed a single-centre, retrospective study of prospectively collected data. We reviewed the cases of adults who underwent primary liver transplantation at the Royal Victoria Hospital in Montréal, Que., between 1990 and 2006. Those receiving retransplants and multi-organ recipients were excluded. Patients who died during the first 3 postoperative months composed the early mortality group. The remaining patients composed the long-term survival group.

We studied a total of 15 parameters:

- recipient's sex
- cause of cirrhosis
- preoperative diagnosis of hepatocellular cancer (HCC)
- recipient's age
- CTP score at the time of transplantation
- MELD score at the time of transplantation
- preoperative total bilirubin
- preoperative creatinine
- preoperative international normalized ration (INR)
- preoperative albumin
- donor's cause of death
- donor's sex
- donor's age
- cold ischemia time (CIT)
- warm ischemia time (WIT)

Statistical analysis

We evaluated all 15 parameters individually for their impact either on actual early mortality (univariate binary logistic regression analysis) or on actuarial long-term patient survival (univariate Cox regression analysis). The parameters that showed statistical significance were incorporated into models for the study of the actual early mortality (multivariate binary logistic regression analysis) and of the actuarial long-term patient survival (multivariate Cox regression analysis). To avoid collinearity, CTP and MELD scores were never used together with their components (bilirubin, creatinine, INR) in the development of multivariate models. We constructed receiver operating characteristic (ROC) curves for all variables that were shown in the multivariate models to have an impact on actual posttransplant early mortality. Statistical analysis was performed with SPSS 16.0 for Mac (SPSS Inc.).

Results

Between 1990 and 2006, 458 primary adult liver transplants were performed. Fifty-seven (12.44%) patients died during the first 3 postoperative months and composed the early mortality group. The remaining 401 patients composed the long-term patient survival group, with a median follow-up of 4.82 years. Of these 401 recipients, 71 (17%) were followed up for more than 10 years, whereas 13 (3.2%) were lost to follow-up.

Of the 103 recipients in whom HCC was diagnosed preoperatively, 47 (45.6%) exceeded the Milan criteria. The categorical parameters that describe this cohort of patients are presented as absolute numbers and percentages (Table 1). The continuous parameters are presented as median values and ranges (Table 2).

Early posttransplant mortality was 12.44%. The incidence of postoperative mortality correlated positively with CTP and MELD scores at the time of transplantation. When studied individually, all components of the MELD score (recipient's bilirubin, recipient's creatinine and recipient's INR) also correlated positively with early posttransplant mortality (Table 2). Of the remaining parameters (Table 1, Table 2), only WIT was identified by the univariate analysis to be associated with early postoperative

mortality. Based on these observations, 2 multivariate models were built (Table 3). In the first one, both the CTP score and WIT had a statistically significant effect on post-transplant mortality. In the second model, both the MELD score and WIT retained their statistical significance. Construction of ROC curves revealed that a CTP score of 12 had a sensitivity of 36% and a specificity of 80% for predicting early mortality (c-statistic 0.633, 95% confidence interval [CI] 0.559–0.708, $p = 0.001$). In addition, a MELD score of 28 had a sensitivity of 45% and a specificity of 81% for predicting early mortality (c-statistic 0.648, 95% CI 0.565–0.730, $p < 0.001$). Finally, a WIT of 1.3 hours had a sensitivity of 20% and a specificity of 81% for predicting early mortality (c-statistic 0.614, 95% CI 0.528–0.699, $p = 0.010$). The aforementioned ROC curves are depicted in Figure 1.

The 10-year long-term actuarial survival was 65%. The parameters that were identified by the univariate analysis to be associated with improved long-term survival were recipient's sex (female), diagnosis of either primary biliary cirrhosis or primary sclerosing cholangitis and recipient's age. On the other hand, diagnosis of HCV cirrhosis and preoperative diagnosis of HCC correlated inversely with long-term survival (Table 4, Table 5). The multivariate model that was built based on these observations (Table 3) revealed that recipient's sex (female) and recipient's age correlated positively with long-term survival, whereas presence of HCC had a negative impact. Interestingly, in the multivariate model, primary diagnosis lost its statistical significance. The impact of recipient's sex on long-term survival is depicted in Figure 2.

Table 1. Categorical parameters associated with early postoperative mortality (< 90 days) after liver transplantation in a cohort of 458 patients*

Parameter	No. (%)	OR (95% CI)	*p* value
Recipient's sex		0.631 (0.357–1.117)	0.11
Female	143 (31.2)		
Male	315 (68.8)		
Cause of liver failure			0.31
Ethanol	87 (19.0)	1.117 (0.540–2.309)	0.76
Hepatitis B virus	45 (9.8)	1.509 (0.519–4.383)	0.45
Hepatitis C virus	186 (40.6)	1.119 (0.675–2.127)	0.54
PBC or PSC	66 (14.4)	1.232 (0.533–2.848)	0.62
Metabolic	14 (3.1)	1.876 (0.241–14.616)	0.55
Drug-induced	6 (1.3)	0.277 (0.050–1.588)	0.14
Other	19 (4.1)	0.376 (0.130–1.087)	0.07
Unknown	35 (7.6)	0.536 (0.223–1.292)	0.16
Diagnosis of HCC		1.419 (0.690–2.918)	0.34
No	355 (77.5)		
Yes	103 (22.5)		
Donor's sex		1.452 (0.810–2.603)	0.21
Female	252 (55.8)		
Male	200 (44.2)		
Donor's cause of death			0.79
CVA	241 (53.4)	1.219 (0.693–2.144)	0.49
Trauma	173 (38.4)	0.848 (0.478–1.505)	0.57
Other	37 (8.2)	0.879 (0.327–2.361)	0.80

CI = confidence interval; CVA = cerebrovascular accident; HCC = hepatocellular cancer; OR = odds ratio; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis.
*Early postoperative mortality was 12.44% ($n = 57$).

Table 2. Continuous parameters associated with early postoperative mortality (< 90 days) after liver transplantation in a cohort of 458 patients*

Parameter	Median (range)	OR (95% CI)	*p* value
Recipient's age, yr	57 (18–75)	1.006 (0.981–1.031)	0.64
CTP score	11 (6–15)	1.319 (1.110–1.567)	0.002
MELD score	20 (6–40)	1.057 (1.032–1.083)	< 0.001
Bilirubin, μmol/L	57.8 (4.8–944.9)	1.003 (1.001–1.004)	0.001
Creatinine, μmol/L	93.00 (42.0–685.0)	1.005 (1.002–1.007)	< 0.001
INR	1.79 (0.93–20.09)	1.170 (1.045–1.310)	0.007
Albumin, g/L	22 (7–51)	0.977 (0.942–1.014)	0.22
Donor's age, yr	47 (3–85)	1.002 (0.987–1.018)	0.75
Cold ischemia time, h	9.75 (0.30–24.00)	1.077 (0.989–1.173)	0.09
Warm ischemia time, h	0.90 (0.20–3.20)	2.601 (1.250–5.413)	0.011

CI = confidence interval; CTP = Child–Turcotte–Pugh; INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; OR = odds ratio.
*Early postoperative mortality was 12.44% ($n = 57$).

Discussion

The issue of allocation of deceased donor organs is not new, and it spans through all types of grafts (e.g., liver, kidney). Two different philosophical approaches have been developed.[14] The first approach, the justice or equity view, maximizes access for all potential candidates and adopts a "sickest first" policy. The second approach, the utility view, strives to maximize graft survival and therefore allocates organs preferentially to the lowest-risk candidates. Ideally,

Table 3. Multivariate analysis models for the prediction of actual early mortality (2 models) and actuarial long-term survival (1 model) after liver transplantation

Analysis; parameter	OR (95% CI)	*p* value
Early mortality predictors		
Multivariate analysis A $n = 407$		
MELD score	1.054 (1.027–1.082)	< 0.001
Warm ischemia time, h	2.944 (1.338–6.479)	0.007
Multivariate analysis B $n = 415$		
CTP score	1.312 (1.088–1.582)	0.004
Warm ischemia time, h	2.823 (1.321–6.033)	0.004
Long-term survival predictors		
Multivariate analysis $n = 397$		
Recipient's sex, female	2.018 (1.236–3.293)	0.005
Cause of cirrhosis	0.964 (0.625–1.487)	0.87
Diagnosis of HCC	0.565 (0.357–0.894)	0.015
Recipient's age	1.022 (1.003–1.042)	0.024

CI = confidence interval; CTP = Child–Turcotte–Pugh; HCC = hepatocellular cancer; MELD = Model for End-Stage Liver Disease; OR = odds ratio.

with a limitless supply of donated organs, a justice allocation system should be implemented. However, since donated grafts are scarce resources, especially now that the increase in demand has been on the part of patients who were previously considered unsuitable for transplantation, the issue of organ utility is gradually more discussed within the transplant community.[15] This debate is furthered fueled by a stipulation in US federal regulation that organ allocation should strive to maximize lifetime benefit.[16] To develop a liver graft allocation system that incorporates the principle of utility, the development of a model that predicts posttransplant outcomes is necessary. Since MELD or CTP scores are unable to accurately predict postoperative patient survival,[5–7,12] identification of preoperative parameters that correlate with outcomes is mandatory. Indeed, it seems implausible that any system, which needs to combine justice and utility in liver graft allocation, would not include donor or other variables that have been shown to be important.[8,10,17]

In the present study, while the incidence of early postoperative mortality correlates positively with either CTP or MELD scores, the c-statistic of the ROC curves was well below 0.7 for both scores. This finding is in agreement with previous literature.[5–7] Warm ischemia time was an independent predictor of early postoperative mortality, but the c-statistic of the relevant ROC curve was again below 0.7. However, WIT might have a place in a model predicting early postoperative mortality after liver transplantation. Actually, WIT is an intraoperative rather than a preoperative parameter. In addition, transplant surgeons always try to achieve the smallest WIT possible and, whenever a long WIT is recorded, intraoperative technical difficulties have been encountered (e.g., poor vascular anastomosis, inadequacy of inflow vessels, ongoing hemorrhage). Moreover, these technical difficulties explain the broad range of WIT and the subsequent wide CI in parametric analysis. However, despite the wide CI in both multivariate analyses, because of the high odds ratios (2.944 and 2.823,

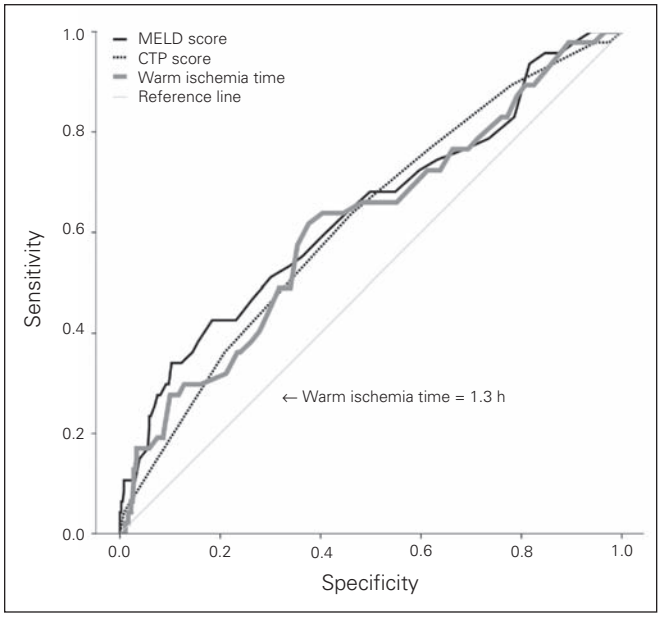

Fig. 1. Most liver transplant recipients who died within the first 90 posttransplant days did not have a significantly longer warm ischemia time (WIT). However, the specificity of a WIT that exceeded 78 minutes (1.3 h) for predicting early postoperative mortality was 81%. MELD = Model for End-Stage Liver Disease; CTP = Child–Turcotte–Pugh.

Table 4. Categorical parameters associated with long-term survival after liver transplantation in a cohort of 401 patients, after exclusion of patients with early postoperative mortality (< 90 days)

Analysis; parameter	No. (%)	OR (95% CI)	*p* value
Recipient's sex		2.216 (1.380–3.558)	< 0.001
Female	120 (29.9)		
Male	281 (70.1)		
Cause of liver failure			0.027
Ethanol	77 (19.2)	0.886 (0.568–1.380)	0.59
Hepatitis B virus	41 (10.2)	1.215 (0.615–2.401)	0.58
Hepatitis C virus	165 (41.1)	0.535 (0.370–0.773)	0.001
PBC or PSC	59 (14.7)	2.629 (1.325–5.179)	0.006
Metabolic	13 (3.2)	1.850 (0.587–5.828)	0.29
Drug induced	4 (1)	0.918 (0.128–6.590)	0.93
Other	14 (3.5)	0.473 (0.066–3.397)	0.46
Unknown	28 (7.0)	1.616 (0.659–3.960)	0.29
Diagnosis of HCC		0.438 (0.297–0.645)	< 0.001
No	308 (76.8)		
Yes	93 (23.2)		
Donor's sex		0.902 (0.624–1.305)	0.59
Female	180 (45.3)		
Male	217 (54.7)		
Donor's cause of death			0.88
CVA	214 (54.0)	0.952 (0.657–1.381)	0.80
Trauma	150 (37.9)	1.094 (0.745–1.608)	0.65
Other	32 (8.1)	0.901 (0.483–1.680)	0.74

CI = confidence interval; CVA = cerebrovascular accident; HCC = hepatocellular cancer; OR = odds ratio; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis.

Table 5. Continuous parameters associated with long-term survival after liver transplantation in a cohort of 401 patients, after exclusion of patients with early postoperative mortality (< 90 days)

Parameter	Median (range)	OR (95% CI)	*p* value
Recipient's age, yr	57 (18–74)	1.028 (1.009–1.047)	0.003
CTP score	11 (6–15)	0.917 (0.830–1.013)	0.09
MELD score	19 (6–40)	0.992 (0.972–1.013)	0.44
Bilirubin, μmol/L	56.2 (4.8–846.0)	1.000 (0.998–1.001)	0.64
Creatinine, μmol/L	93 (42–635)	1.000 (0.998–1.002)	0.96
INR	1.78 (0.93–13.13)	0.948 (0.831–1.081)	0.42
Albumin, g/L	22 (7–51)	1.013 (0.989–1.038)	0.29
Donor's age, yr	46 (3–80)	1.011 (1.000–1.022)	0.06
Cold ischemia time, h	9.75 (0.30–24.00)	1.034 (0.977–1.095)	0.25
Warm ischemia time, h	0.89 (0.20–3.20)	1.193 (0.639–2.225)	0.58

CI = confidence interval; CTP = Child–Turcotte–Pugh; INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; OR = odds ratio.

respectively) WIT-based nomograms for predicting posttransplant mortality should be developed and validated in large (ideally multicentre) patient cohorts. In this way, calculation of the maximum allowable WIT for a specific recipient, graft combination will become feasible, with all its implications for the training of transplant fellows and for the intraoperative surgical performance.

Female sex was among the parameters that were identified to be independent predictors of improved long-term survival. Previously, female sex has been associated with increased recipient survival.[18,19] Absence of HCC was associated, as anticipated, with improved long-term survival. This is particularly true for this specific patient cohort, since almost half of the recipients with diagnoses of HCC exceeded Milan criteria.[20] An interesting finding was the observation that older recipients tended to have a slightly better long-term survival (odds ratio 1.022). Most likely this is a curiosity of statistics, since it is hard to explain the finding pathophysiologically and since many authors have reported the opposite result.[21] On the other hand, it was surprising to find that HCV cirrhosis was not associated with statistically inferior long-term survival. The satisfactory survival curves in patients with HCV might be explained by the antithymocyte globulin induction/low maintenance immunosupression policy followed in our centre, which is suggested to be associated with good outcomes in this particular patient population.[22]

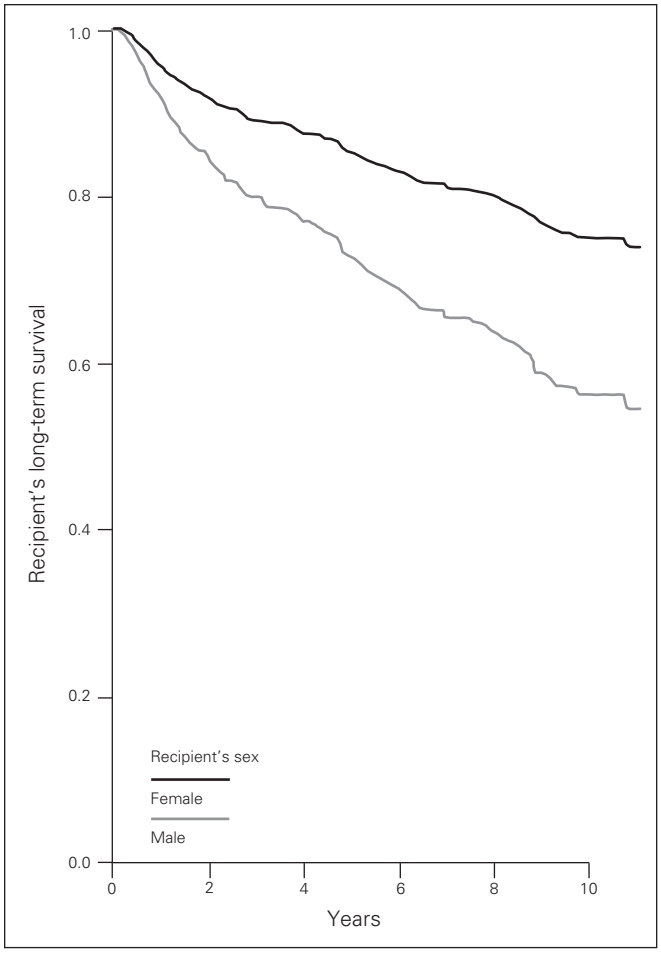

Fig. 2. Patient long-term survival after liver transplantation, stratified by recipient's sex, adjusted for primary diagnosis, presence of hepatocellular cancer and recipient's age. Early posttransplant deaths (n = 57), mainly due to technical complications, were excluded.

Conclusion

The CTP or MELD scores, in conjunction with WIT, might have a role in predicting early postoperative mortality after liver transplantation. On the other hand, recipient sex and absence of HCC are associated with improved long-term survival.

Competing interests: None declared.

Contributors: Drs. Vrochides, Tchervenkov and Wong designed the study. Drs. Vrochides, Hassanain, Chaudhury, Ghali and Chan acquired the data, which Drs. Vrochides, Hassanain, Barkun, Paraskevar, Chantarovich and Deschenes analyzed. Drs. Vrochides and Hassanain wrote the article, which all other authors reviewed. All authors approved the final version for publication.

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