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Original Research

Material deprivation affects the management and clinical outcome of hepatocellular carcinoma in a high-resource environment

Alessandro Cucchetti [a,b], Annagiulia Gramenzi [c,*], Philip Johnson [d], Edoardo G. Giannini [e], Francesco Tovoli [f], Gian Ludovico Rapaccini [g], Fabio Marra [h], Giuseppe Cabibbo [i], Eugenio Caturelli [j], Antonio Gasbarrini [k], Gianluca Svegliati-Baroni [l], Rodolfo Sacco [m], Marco Zoli [n], Filomena Morisco [o], Maria Di Marco [p], Andrea Mega [q], Francesco G. Foschi [r], Elisabetta Biasini [s], Alberto Masotto [t], Gerardo Nardone [u], Giovanni Raimondo [v], Francesco Azzaroli [w], Gianpaolo Vidili [x], Maurizia R. Brunetto [y], Fabio Farinati [z], Franco Trevisani [c] for the Italian Liver Cancer (ITA.LI.CA) Group[1]

[a] *Department of Medical and Surgical Sciences, University of Bologna, Italy*
[b] *Morgagni-Pierantoni Hospital, Forlì, Italy*
[c] *Department of Medical and Surgical Sciences, Semeiotica Medica Unit, University of Bologna, Italy*
[d] *Department of Molecular and Clinical Cancer Medicine, University of Liverpool, UK*
[e] *Department of Internal Medicine, Gastroenterology Unit, IRCCS Policlinico San Martino, University of Genova, Italy*
[f] *Internal Medicine Unit, S. Orsola-Malpighi Hospital, Bologna, Italy*
[g] *Department of Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario "A. Gemelli", IRCCS, Roma, Italy*
[h] *Department of Experimental and Clinical Medicine, University of Firenze, Italy*
[i] *Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), Section of Gastroenterology and Hepatology, University of Palermo, Italy*
[j] *Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy*
[k] *Internal Medicine and Gastroenterology Unit, Fondazione Policlinico Universitario "A. Gemelli", IRCCS, Roma, Italy*
[l] *Department of Gastroenterology, Polytechnic University of Marche, Ancona, Italy*
[m] *Gastroenterology and Digestive Endoscopy, Foggia University Hospital, Foggia, Italy*

* *Corresponding author*: Dipartimento di Scienze Mediche e Chirurgiche, Semeiotica Medica, Alma Mater Studiorum, Università di Bologna, Via Albertoni 15, 40138 Bologna, Italy. Fax: +39 0512142930.

E-mail address: alessandro.cucchett2@unibo.it (A. Cucchetti), annagiulia.gramenzi@unibo.it (A. Gramenzi), philip.johnson@liverpool.ac.uk (P. Johnson), egiannini@unige.it (E.G. Giannini), francesco.tovoli2@unibo.it (F. Tovoli), gianludovico.rapaccini@policlinicogemelli.it (G.L. Rapaccini), fabio.marra@unifi.it (F. Marra), giuseppe.cabibbo78@gmail.com (G. Cabibbo), ecaturelli@tiscalinet.it (E. Caturelli), antonio.gasbarrini@policlinicogemelli.it (A. Gasbarrini), g.svegliati@univpm.it (G. Svegliati-Baroni), saccorodolfo@hotmail.com (R. Sacco), marco.zoli@unibo.it (M. Zoli), filomena.morisco@unina.it (F. Morisco), mariellladimarco@gmail.com (M. Di Marco), andrea.mega@sabes.it (A. Mega), francesco.foschi@auslromagna.it (F.G. Foschi), ebiasini@ao.pr.it (E. Biasini), alberto.masotto@sacrocuore.it (A. Masotto), nardone@unina.it (G. Nardone), raimondo@unime.it (G. Raimondo), francesco.azzaroli@unibo.it (F. Azzaroli), gianpaolovidili@uniss.it (G. Vidili), brunetto@med-club.it (M.R. Brunetto), fabio.farinati@unipd.it (F. Farinati), franco.trevisani@unibo.it (F. Trevisani).

[1] Members of the ITA.LI.CA group are listed in Appendix section.

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[n] Department of Medical and Surgical Sciences, Internal Medicine Unit, University of Bologna, Italy
[o] Department of Medicine and Surgery, Gastroenterology Unit, University of Napoli "Federico II", Italy
[p] Medicine Unit, Bolognini Hospital, Seriate, Italy
[q] Gastroenterology Unit, Bolzano Regional Hospital, Bolzano, Italy
[r] Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Italy
[s] Infectious Diseases and Hepatology Unit, Azienda Ospedaliero-Universitaria di Parma, Italy
[t] Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy
[u] Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Napoli "Federico II", Italy
[v] Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina, Italy
[w] Department of Medical and Surgical Sciences, Gastroenterology Unit, University of Bologna, Italy
[x] Department of Medical, Surgical and Experimental Sciences, Clinica Medica Unit, University of Sassari, Italy
[y] Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory and Internal Medicine, University of Pisa, Italy
[z] Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy

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Abstract ***Aim:*** This study investigated how material deprivation in Italy influences the stage of hepatocellular carcinoma (HCC) at diagnosis and the chance of cure.
Methods: 4114 patients from the Italian Liver Cancer database consecutively diagnosed with HCC between January 2008 and December 2018 were analysed about severe material deprivation (SMD) rate tertiles of the region of birth and region of managing hospitals, according to the European Statistics on Income and Living Conditions. The main outcomes were HCC diagnosis modalities (during or outside surveillance), treatment adoption and overall survival.
Results: In more deprived regions, HCC was more frequently diagnosed during surveillance, while the incidental diagnosis was prevalent in the least deprived. Tumour characteristics did not differ among regions. The proportion of patients undergoing potentially curative treatments progressively decreased as the SMD worsened. Consequently, overall survival was better in less deprived regions. Patients who moved from most deprived to less deprived regions increased their probability of receiving potentially curative treatments by 1.11 times (95% CI 1.03 to 1.19), decreasing their mortality likelihood (hazard ratio 0.78 95% CI 0.67 to 0.90).
Conclusions: Socioeconomic status measured through SMD does not seem to influence HCC features at diagnosis but brings a negative effect on the chance of receiving potentially curative treatments. Patient mobility from the most deprived to the less deprived regions increased the access to curative therapies, with the ultimate result of improving survival.

1. Introduction

The relationship between socio-economic status and health is well-documented [1–3]. In addition, several studies have consistently reported a progressive increase in both all-cause and cancer mortality based on the degree of material deprivation in different geographic areas of the world [4–6]. Material deprivation measures poverty by considering not only the financial resources available but also the broader aspects of the standard of living. It expresses the inability to afford certain 'basic' items, considered by most people as desirable or even necessary, to lead a life adequate to financial pressures and economic strains [4–6].

In the European Union (EU), liver cancer is one of the five most common cancers, with hepatocellular carcinoma (HCC) accounting for over 80% of them [7,8]. Statistics from the UK Cancer Research Program showed that the incidence of liver cancer in males is 107% higher in the most deprived areas than in the least deprived. Furthermore, in the most deprived areas, liver cancer mortality is 100% higher for males and 72% higher for females when compared with the least deprived [9]. Although these data indicate that deprivation affects both liver cancer incidence and mortality, the underlying reasons received little attention.

The main determinants of survival after the diagnosis of HCC are stage, the accuracy of staging and the optimisation of available therapies [7,10–12]. Tumour incidence and local resources inevitably influence all these variables. Generally, the higher the incidence of a disease, the better the healthcare pathway for its screening, diagnosis and therapy. In Europe, Italy ranks as the country with the highest incidence of HCC

with an estimated number of patients diagnosed with HCC of about 10.000 each year [7]. The guidelines of the World Gastroenterology Organization on HCC define high-resource countries as those in which liver transplantation (LT) is available [11,12] and, consequently, Italy represents a high-resource environment. However, there are important economic and social inequalities between Italian regions [13,14], and these differences have an impact on the path leading from HCC prevention to early diagnosis and access to optimal treatment. For several decades, these inequalities have generated a problem of interregional health mobility that moves patients from the poorest to the least disadvantaged regions in search of diagnoses and/or procedures that are absent or not immediately accessible in their own regions [15,16].

The present study evaluated how material deprivation influences the stage of HCC at diagnosis, the access to potentially curative treatments and the life expectancy after detection in one of the EU countries burdened with the highest incidence of this cancer.

2. Methods

Data collected in the 'Italian Liver Cancer' (ITA.LI.CA) database were used for the present study. Since 1987, ITA.LI.CA prospectively collected data on patients diagnosed with HCC and treated in 23 Italian centres. Data entry is updated every 2 years and their consistency is regularly checked by a dedicated coordinator. ITA.LI.CA complies with Regulation 2016/679 of the European Parliament on the protection of personal data and with the ethical guidelines of the Declaration of Helsinki. Out of the total of 7705 patients with HCC since 1987, 5196 patients diagnosed between January 2008 and December 2018 were selected. As 867 patients were missing details regarding the region of origin and 215 patients were still awaiting complete data entry, the present study included 4114 cases.

Surveillance for HCC based on liver ultrasound (with or without α-fetoprotein determination) performed every 6 ± 1 or 12 ± 1 months was offered to patients considered at-risk according to European and national recommendations concisely, patients with cirrhosis in Child-Pugh class A and B, or C if transplantation was a possible option, patients with chronic hepatitis B or those with liver fibrosis $\geq$ F3 [7,17–19]. HCC was diagnosed by histology in 647 cases (15.7%) and typical imaging features according to the international guidelines in the remaining [7,17]. Tumour number and size, vascular invasion and metastatic spread were assessed by computed tomography or magnetic resonance. The choice of therapy was guided by the EASL recommendations, modified according to the characteristics, circumstances and preferences of the individual patient, after review by local multidisciplinary teams considering the availability and/or accessibility of the various therapeutic options within their region. Consequently, the distribution of therapies in the participating centres was expected to be non-homogeneous [20]. Treatments were ranked hierarchically from the most to the least effective as follows, LT, hepatic resection (HR), percutaneous ablation (ABL) either with ethanol injection, radiofrequency or microwave, intra-arterial therapies, sorafenib and best supportive care. Transplantation, HR and ABL were considered as potentially curative treatments [21].

2.1. Material deprivation rate

According to the European Statistics on Income and Living Conditions, the material deprivation rate reflects an individual's ability to afford certain items widely considered desirable for an adequately fulfilled life [22]. Severe material deprivation (SMD) rate is defined as the inability to afford at least four of the following:

1. To pay rent, mortgage or utility bills
2. To keep home adequately warm
3. To face unexpected expenses
4. To eat meat or proteins regularly
5. To go on holiday
6. To have a television set
7. To have a washing machine
8. To have a car
9. To have a telephone.

Between 2008 and 2018, the average SMD rate of the EU was 8.7%. The average percentage of individuals included in this study (2008–2018) fulfilling the SMD definition by Italian regions is reported in Fig. 1. Based on SMD tertiles, Italian regions were classified as least deprived (Q1), intermediate deprived (Q2) and most deprived (Q3).

2.2. Inter-regional health mobility

For each hospital, the corresponding region was matched with the corresponding SMD tertile by year of diagnosis. For each patient, the region of birth was matched, with the corresponding SMD tertile by year of diagnosis. Between 1952 and 2018, the Italian National Statistics Institute (ISTAT) estimated an inter-regional residence transfer ranging from a maximum of 3.2% between the 1950s and 1960s to an average of 1.8% between 2008 and 2018 [23]. Therefore, the region of birth corresponded to the region of residence at the time of diagnosis with more than 95% of certainty. Patients decided to remain in their region of birth for HCC diagnosis and/or treatment or to move to hospitals located in different regions to access different healthcare resources, and this represents the interregional health mobility that weights on our country [15,16].

Fig. 1. Average distribution of the severe material deprivation ratio between different regions in Italy between 2008 and 2018. Three areas were identified based on severe material deprivation tertiles: least deprived (Q1), intermediate deprived (Q2) and most deprived (Q3). The same region may have belonged to different tertiles between 2008 and 2018 (e.g. Abruzzo belonged to Q1 for one year (2012), to Q2 for 7 years and to Q3 for 4 years).

2.3. Statistical analysis

Missing data for covariates were <10% and replaced using the maximum likelihood estimation method [21]. Pearson's chi-square test or simple regression were adopted when searching for relationships between variables and deprivation. In analysing probabilities of receiving surveillance or potentially curative therapies, a binomial regression (simple generalised linear model) was applied. Multinomial logistic regression was used to investigate the effect of medical migration on different probabilities of receiving each treatment. Overall survival (OS) was computed from HCC diagnosis until death (from any cause) or last follow-up visit. For patients diagnosed during surveillance, lead-time bias correction was applied according to Duffy et al. [24] and

Cucchetti et al. [25]. Cox regression was applied to verify the determinants of survival. For each regression applied, variables with $p < 0.10$ at the univariate approach were included in the multivariable analyses.

3. Results

Characteristics of the 4114 patients with HCC in the study are reported in Table 1. Based on SMD of Italian regions, 1350 patients (32.8%) belonged to Q1, 1067 to Q2 (25.9%) and 1697 to Q3 (41.3%). At the time of HCC diagnosis, the more deprived the region of birth, the younger the patients were, and the higher the proportion suffering from chronic hepatitis B or C ($p < 0.001$). Conversely, non-alcoholic steatohepatitis or alcoholic liver disease were more prevalent in the less deprived regions of birth ($p < 0.001$; Table 1). Patients from least deprived regions were more frequently diagnosed incidentally, during investigation for some other complaint, than those from other regions ($p < 0.001$), whereas patients from more deprived regions were more frequently diagnosed during surveillance ($p < 0.001$). The symptomatic diagnosis was similarly distributed through regions.

Most patients were diagnosed and treated in hospitals located in their own regions. Nevertheless, this proportion progressively decreased as the deprivation worsened. Indeed, 93.6% of patients in Q1, 87.8% in Q2 and 61.4% in Q3 were treated locally ($p < 0.001$). The end result of patient mobility was that 1716 patients (41.7%) were managed in hospitals located in Q1, 1319 patients in hospitals in Q2 (32.1%) and 1079 patients in hospitals in Q3 (26.2%).

Tumour features were similar when stratified by hospitals belonging to different regions (Table 2). However, the more deprived the hospitals' region, the lower the proportion of patients submitted to potentially curative therapies. Indeed, in hospitals located in Q1, 56.9% of patients received potentially curative therapy, this proportion was 51.6% in hospitals located in Q2 and 50.3% in hospitals in Q3 ($p < 0.001$). Median OS was higher in the less deprived regions, ranging from 42.2 months in the least to 35.2 months in the most deprived regions ($p = 0.008$).

The likelihood of being diagnosed with HCC during surveillance (Table 3) was higher for females, for patients with model for end-stage liver disease score ≤ 10, and for those bearing viral hepatitis regardless of patients' regions ($p < 0.05$ for all these conditions in each region). Mobility toward less or more deprived regions did not affect the probability of being diagnosed during surveillance.

As expected, the adoption of potentially curative treatments (Table 4) mostly depended on model for end-stage liver disease score, tumour burden, performance status and presence of neoplastic vascular invasion, with a similar magnitude across different regions ($p < 0.05$ for each variable in each region). At multivariable analysis, the mobility from the most deprived regions toward less deprived regions increased the probability of receiving potentially curative treatments by 1.11 times (95% CI: 1.03–1.19, $p = 0.006$), independently from other features.

Table 1
Epidemiological and clinical characteristics of 4114 patients diagnosed with HCC between January 2008 and December 2018 by SMD tertiles.

Variables	Region of birth of patients[a]			p-value[b]
	Least deprived (n = 1350)	Intermediate deprived (n = 1067)	Most deprived (n = 1697)	
Age [years, mean (SD)]	69.0 (11.2)	67.6 (12.9)	66.9 (12.1)	<0.001
>65 years	901 (66.7%)	673 (63.1%)	1054 (62.1%)	0.009
Male gender	1070 (79.3%)	826 (77.4%)	1297 (76.4%)	0.065
Aetiology[c]				
Hepatitis C	597 (44.2%)	562 (52.7%)	1004 (59.2%)	<0.001
Hepatitis B	110 (8.2%)	98 (9.2%)	213 (12.6%)	<0.001
NASH	211 (15.6%)	124 (11.6%)	169 (9.9%)	<0.001
Alcohol	427 (31.6%)	229 (21.5%)	214 (12.6%)	<0.001
PBC/Other	149 (11.0%)	131 (12.3%)	187 (11.0%)	0.936
MELD [score, mean (SD)]	10.1 (3.9)	10.4 (3.7)	10.1 (3.8)	0.952
>10	431 (31.9%)	407 (38.1%)	559 (32.9%)	0.696
Diagnosis modality				
Surveillance[d]	706 (52.3%)	558 (52.3%)	1035 (61.0%)	<0.001
Incidental	473 (35.0%)	348 (32.6%)	475 (28.0%)	<0.001
Symptoms	171 (12.7%)	161 (15.1%)	187 (11.0%)	0.128

SD = standard deviation; PBC = primary biliary cirrhosis; NASH = non-alcoholic steatohepatitis; MELD = model for end-stage liver disease (= 9.57xln (creatinine (mg/dL)) + 3.78xln (bilirubin (mg/dL)) + 11.2xln(INR) + 6.43 [7]).

[a] Region of birth represents the region of residence with a certainty of >95% according to national statistics [22].

[b] P-value for linear trend.

[c] One patient can have more than one cause of liver disease, consequently the sum of proportions does not sum 100%.

[d] Patients with viral hepatitis had HCC diagnosed through surveillance in 1655 cases out of 2559 (64.7%), whereas non-viral patients had surveillance in 644 cases out of 1555 (41.4%; $p < 0.001$).

Table 2
Tumour features, adoption of potentially curative treatments and survival[a] in the 4114 patients according to the regional deprivation of the managing hospital.

Variables	Region of the hospital			p-value[b]
	Least deprived (n = 1716)	Intermediate deprived (n = 1319)	Most deprived (n = 1079)	
Tumour size [cm, (mean, SD)]	3.8 (2.8)	3.9 (2.9)	3.6 (2.6)	0.102
Tumour number				
Single	978 (57.0%)	742 (56.3%)	610 (56.5%)	0.779
2–3 nodules	552 (32.2%)	434 (32.9%)	360 (33.4%)	0.501
>3 nodules	186 (10.8%)	143 (10.8%)	109 (10.1%)	0.567
Presence of MaVI	203 (11.9%)	160 (12.2%)	128 (11.9%)	0.947
Within Milan criteria[c]	1103 (64.3%)	818 (62.0%)	718 (66.5%)	0.343
ECOG 0–1	1553 (90.5%)	1169 (88.6%)	956 (88.6%)	0.085
Potentially curative therapies	977 (56.9%)	680 (51.6%)	543 (50.3%)	<0.001
Survival [mo, (median, 95% CI)][a]	42.2 (38.2–46.9)	38.3 (35.5–45.1)	35.2 (31.2–41.2)	0.008

SD = standard deviation; ECOG = Eastern cooperative oncology group (0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [7]); MaVI = macroscopic (neoplastic) vascular invasion; mo = months.
[a] Survival was adjusted for lead-time bias for patients diagnosed through surveillance.
[b] P-value for linear trend.
[c] Identified patients with single tumour ≤5 cm or no more than 3 tumours ≤3 cm, without MaVI or extra-hepatic spread.

Details on the likelihood of receiving each therapy with mobility are reported in Fig. 2. Mobility from Q1 toward more deprived regions returned a −6.8% probability of undergoing ABL (p = 0.011) and a +2.9% probability of receiving palliative therapies (p = 0.041). Patients from the Q2 regions had a −2.4% probability of receiving palliative therapies if they moved toward Q1 (p = 0.002). Finally, patients who moved from Q3 to less deprived regions increased their probabilities of LT of +2.5% (p = 0.003) and of HR of +6.9% (p = 0.007).

When OS was stratified by patients' deprivation region of birth, no differences were observed among deprivation tertiles. The median OS was 42 months (95% CI: 37.3–47.5) for patients belonging to Q1, 36.2 months (95% CI: 29.1–42.3) for Q2 and 39.2 months (95% CI: 31.1–44.3) for Q3 (p = 0.108).

Determinants of survival (Table 5) were age, tumour burden, liver function, performance status and neoplastic vascular invasion, with a similar magnitude through different regions (p < 0.05 for each variable in each region). At multivariable analysis, for patients belonging to the most deprived regions, the possibility of travelling to a less deprived region increased survival probabilities, being the adjusted mortality hazard ratio of 0.78 (95% CI: 0.67–0.90 p = 0.001).

4. Discussion

The landmark study of Preston et al. in 1975, established the relationship between national income and life expectancy [26]. This is expected at the population level, as the protective effects of income are substantial. However, the present study focused on patients with HCC suggests that there are other aspects to consider when evaluating how socioeconomic status can affect health.

Table 3
Relative risk of hepatocellular carcinoma diagnosis through surveillance, according to different material deprivation regions and patients' characteristics.

	Region of birth of patients[a]		
	Least deprived (n = 1350)	Intermediate deprived (n = 1127)	Most deprived (n = 1785)
Age ≤ 65 years	0.93 (0.83–1.04)	0.95 (0.85–1.09)	0.99 (0.98–1.01)
Female	1.25 (1.14–1.39)†	1.22 (1.10–1.37)†	1.09 (1.03–1.15)‡
Viral hepatitis	1.51 (1.35–1.70)†	1.67 (1.45–1.92)†	1.38 (1.25–1.53)†
MELD ≤ 10	1.15 (1.03–1.28)‡	1.22 (1.09–1.39)‡	1.11 (1.02–1.20)‡
Mobility to more deprived regions	0.79 (0.61–1.02)	0.98 (0.81–1.19)	–
Mobility to less deprived regions	–	0.86 (0.52–1.39)	0.96 (0.89–1.04)

† <0.001; ‡ <0.05.
MELD = model for end-stage liver disease (= 9.57xln (creatinine (mg/dL)) + 3.78xln (bilirubin (mg/dL)) + 11.2xln(INR) + 6.43 [7]).
[a] Region of birth represents the region of residence with a certainty of >95% according to national statistics [23]. Numbers in parenthesis represent 95%, confidence bands. Results derived from simple generalised linear models for the binomial family regression of each variable with p > 0.10 or from the moment of exit at the backward selection of multivariable approach when p > 0.10. Each univariable result is omitted for simplicity. Reference conditions of RR values were the absence of the condition reported here. For mobility, the reference condition was where the region of birth and region in which the hospital was situated were in the same deprivation tertile.

Table 4
Relative risk of receiving potentially curative treatments according to different material deprivation regions and patients' characteristics.

Variables	Region of birth of patients[a]		
	Least deprived (n = 1350)	Intermediate Deprived (n = 1127)	Most Deprived (n = 1785)
Age ≤ 65 years	1.04 (0.94–1.14)	1.04 (0.92–1.17)	1.09 (0.98–1.19)
Female	1.01 (0.92–1.11)	1.05 (0.92–1.20)	1.04 (0.93–1.15)
Viral hepatitis	1.12 (0.98–1.22)	1.09 (0.96–1.23)	1.08 (0.99–1.18)
MELD ≤ 10	1.22 (1.09–1.35)†	1.29 (1.15–1.47)†	1.31 (1.18–1.46)‡
Within Milan criteria[b]	1.36 (1.22–1.51)†	1.50 (1.31–1.72)†	1.55 (1.38–1.74)†
ECOG 0–1	1.89 (1.41–2.55)†	2.62 (1.78–3.86)†	2.48 (1.74–3.54)†
Absence of MaVI	5.26 (3.19–8.66)†	3.24 (2.06–5.12)†	3.87 (2.56–5.84)†
Mobility to more deprived regions	0.86 (0.67–1.07)	1.01 (0.84–1.23)	–
Mobility to less deprived regions	–	0.98 (0.63–1.52)	1.11 (1.03–1.19)‡

† <0.001; ‡ <0.05.
MELD = model for end-stage liver disease; SD = standard deviation; PBC = primary biliary cirrhosis; NASH = non-alcoholic steatohepatitis; MELD = model for end-stage liver disease (= 9.57xln (creatinine (mg/dL)) + 3.78xln (bilirubin(mg/dL)) + 11.2xln(INR) + 6.43 [7]); ECOG = Eastern Cooperative Oncology Group (0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [7]); MaVI = macroscopic (neoplastic) vascular invasion.
[a] Region of birth represents the region of residence with a certainty of >95% according to national statistics [23]. Numbers in parenthesis represent 95%, confidence bands. Results derived from simple generalised linear models for the binomial family regression of each variable with $p > 0.10$ or from the moment of exit at the backward selection of multivariable approach when $p > 0.10$. Each univariable result is omitted for simplicity. Reference conditions of RR values were the absence of the condition reported here. For mobility, the reference condition was where the region of birth and region in which the hospital was situated were in the same deprivation tertile.
[b] Identified patients with single tumour ≤5 cm or no more than 3 tumours ≤3 cm, without MaVI or extra-hepatic spread.

World Bank classified Italy as a 'high-income economy' country [27] and with more than 20 LT centres Italy has high resources for the treatment of HCC [11,12]. However, Italy suffers from income disparities. The European Statistical Office currently places Italy's income inequality ratio above the EU average, and the most deprived Italian regions have SMD rates such as those of lower-income countries such as Greece, Lithuania and Hungary [28].

Our study shows that HCC survival was related to deprivation when deprivation tertiles were identified by hospitals' regions but not by patients' regions. Therefore, from the patients' perspective, determinants of mortality for HCC are more complex than simply geographical origin, and the phenomenon of inter-regional health mobility represents a backbone of them. Indeed, a remarkable proportion of patients moved from more deprived regions toward hospitals of less deprived ones in search of better healthcare [14,15]. In the most deprived area, this phenomenon occurred in up to 40% of cases, reversing the proportions between the patients' origin region and hospital region. Accordingly, although most HCC cases came from more deprived regions, most of them were managed in a hospital located in less deprived regions where the chances of receiving potentially curative therapies increased by 4–8% and, even more importantly, median OS increased by about 12 months.

Having identified a geographic variation with important public health implications, we looked at the possible causes. First, the chance of cure was not determined by access to diagnostic facilities. When stratified by patient' region of birth, the diagnosis of HCC was obtained more frequently during surveillance in the most deprived regions, possibly because of the higher prevalence of chronic viral hepatitis, for which guidelines indicate exactly when patients should enter a surveillance program [17,19]. When they were reorganised by hospitals' regions, no differences were observed with respect to tumour characteristics or diagnostic modality. However, the more deprived the region of hospitals, the lower the proportion of patients undergoing potentially curative therapies and the mobility from these toward hospitals in the least deprived regions increased the possibility of receiving such therapies. The exact opposite occurred when health mobility had the reverse direction.

Patients moved from more deprived to less deprived regions were more likely to receive LT and HR, while the ABL rate remained unchanged. It is possible that there is a different referral rate to a liver or transplant surgeon between most and least deprived regions or that surgeons act differently between regions. That is, patients with HCC who were not ideal candidates for HR or LT in their own regions may have moved to less deprived regions capable of incurring higher costs for additional preoperative assessments and prolonged postoperative courses [29–31]. On the opposite, mobility from less to more deprived regions reduced the likelihood (−6.8%) of being treated with ABL, which is mainly indicated for small tumours [7], probably shifting patients to surgery (+5.1%), which is easier in small superficial lesions that require a more challenging ablation approach [32]. Alternatively, even though these patients had small tumours, they were not considered ideal surgical candidates and consequently moved to intra-arterial therapies (+5.7%).

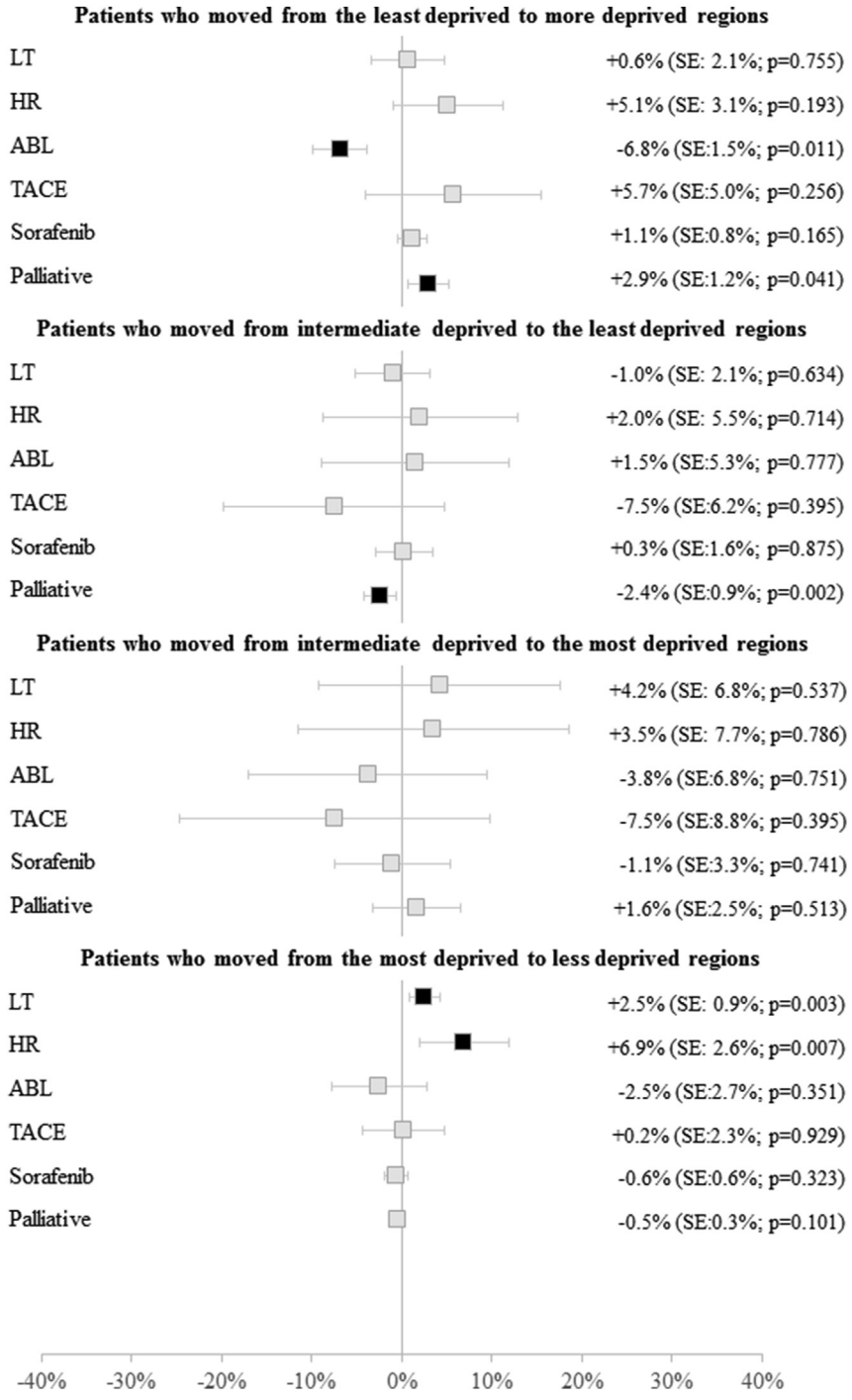

Fig. 2. Results from multinomial logistic regression model showing that the probability of receiving a given treatment was modified by patients' mobility across different deprived regions.

For LT, the scenario is more complex. In Italy, there is great variability in the rate of organ donation between the most deprived (lowest) and the least deprived (highest) regions [33]. Furthermore, the graft allocation system varies between different areas so that donated organs are not distributed with a unique system at the national level [32]. Consequently, the scarcity of donors negatively affects the feasibility of LT in centres located in the most deprived regions [33], while centres in the least deprived regions can transplant even patients from other regions, thanks to the higher donation rate and greater use of extended transplantation criteria and down-staging procedures [34,35]. Obviously, this policy is expensive and considering the large remarkable proportion of patient's mobility toward less deprived regions (38.6% in our study); it is affordable only for

Table 5
Hazard ratios for overall survival according to different material deprivation regions and patients' characteristics.

Variables	Region of birth of patients[a]		
	Least deprived (n = 1350)	Intermediate deprived (n = 1127)	Most deprived (n = 1785)
Age ≤ 65 years	0.77 (0.64–0.91)†	0.86 (0.73–0.98)‡	0.76 (0.66–0.86)†
Female	0.96 (0.79–1.17)	0.84 (0.68–1.04)	1.06 (0.90–1.25)
Viral hepatitis	0.90 (0.77–1.05)	0.92 (0.77–1.09)	0.89 (0.77–1.04)
MELD ≤ 10	0.57 (0.48–0.67)†	0.54 (0.46–0.65)†	0.60 (0.59–0.81)†
Within Milan criteria[b]	0.74 (0.62–0.87)†	0.74 (0.62–0.88)†	0.69 (0.59–0.81)†
ECOG 0–1	0.52 (0.41–0.65)†	0.42 (0.33–0.54)†	0.48 (0.38–0.59)†
Absence of MaVI	0.30 (0.24–0.38)†	0.41 (0.32–0.52)†	0.32 (0.27–0.40)†
Mobility to more deprived regions	1.13 (0.83–1.52)	1.10 (0.84–1.44)	–
Mobility to less deprived regions	–	0.82 (0.41–1.66)	0.78 (0.67–0.90)‡

† <0.001; ‡ <0.05.
MELD = model for end-stage liver disease (= 9.57xln (creatinine (mg/dL)) + 3.78xln (bilirubin (mg/dL)) + 11.2xln(INR) + 6.43 [7]); ECOG = Eastern Cooperative Oncology Group (0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [7]); MaVI = macroscopic (neoplastic) vascular invasion.
[a] Region of birth represents the region of residence with a certainty of >95% according to national statistics [23]. Numbers in parenthesis represent 95%, confidence bands. Results derived from simple Cox regression of each variable with $p > 0.10$ or from the moment of exit at the backward selection of multivariable approach when $p > 0.10$. Each univariable result is omitted for simplicity. Reference conditions of HRs were the absence of the condition reported here. For mobility, the reference condition was where the region of birth and region in which the hospital was situated were in the same deprivation tertile.
[b] Identified patients with single tumour ≤5 cm or no more than 3 tumours ≤3 cm, without MaVI or extra-hepatic spread.

regions with the highest total health expenditure per capita.

The major limitations of this study are the extent to which our population is representative of the whole Italian HCC population and the sample size of some subgroups. First, from European and national statistics [7,8,36,37], about 10.000 HCC cases are expected each year, and the present study enrolled only about 6% of all potential patients. However, ITA.LI.CA is the largest dataset on HCC available in our country, with all reported clinical and treatment features; therefore, we can, unfortunately, state that the largest part of potential data is currently lost. Analysing data provided by national statistics for 2008–2018, by patients' region of residence [36,37], we observed that the least deprived regions had an SMD index of 5.6% and mortality for liver cancers of 15.0/100.000 inhabitants and that this figure was comparable to that observed in the most deprived regions of 14.5/100.000 but in the presence of an SMD of 15.5%. Intermediate deprived regions had a mortality of 11.5/100.000 with an SMD of 7.2%. Thus, there was no clear relationship between SMD and mortality by *patient* region of residence, indicating that national data support that the simple segregation of survival according to the deprivation tertile of patients' region did not produce clear differences. Nevertheless, a relation between deprivation and mortality ensued when our results were segregated by *hospital* region. All these aspects are because of inter-regional health mobility. Consequently, our findings might be likely representative of most of the HCC diagnosed in Italy. The second limitation concerns the subgroup of patients who moved from the least to the more deprived regions, representing only 6.4% (86 patients) of the 1350 patients forming this tertile. We acknowledge that data on treatment migration reported in Fig. 2 should be considered with caution.

In conclusion, our study shows that, in a country like Italy, with a 'high-income economy' but also with regional income inequalities, a stringent relationship between material deprivation and outcome of HCC exists mainly because of the access to potentially curative treatments rather than to the timing of cancer diagnosis. Inter-regional mobility from the most deprived regions to hospitals of less deprived areas in search of better healthcare is, unfortunately, a common phenomenon in our country, resulting in an increased chance to undergo curative therapies and in improved survival. This phenomenon mitigates the survival gap existing among regions with different degrees of material deprivation.

These findings provide an important message in arranging policies regarding national health systems. They should prompt strategies aimed to equipoise the chance of having the best management regardless of the area where the patient lives or, alternatively, to convey all patients with HCC toward centres with the highest resources and proficiency.

Authors contributions

AC conceived and designed the study, searched the literature, interpreted the results and wrote the manuscript. Annagiulia Gramenzi, PJ and Franco Trevisani discussed and interpreted the results, wrote and edited the manuscript. AC and PJ undertook the statistical analysis. EGG, Francesco Tovoli, GLR, FM, GC, EC, Antonio Gasbarrini, GSB, RS, MZ, FM, MDM, Andrea Mega, FGF, EB, Alberto Masotto, GN, GR,

FA, GV, MRB, FF were all responsible for ITA.LI.CA data collection and update. All authors critically revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Franco Trevisani, as ITA.LI.CA coordinator, is the guarantor.

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Conflict of interest statement

None.

Appendix – Other members of the ITA.LI.CA group

Department of Medical and Surgical Sciences, Semeiotics Unit, University of Bologna: Francesca Avanzato, Maurizio Biselli, Paolo Caraceni, Francesca Garuti, Annagiulia Gramenzi, Andrea Neri, Valentina Santi.

Department of Surgery, Oncology and Gastroenterology, University of Padova: Filippo Pellizzaro, Angela Imondi, Anna Sartori, Barbara Penzo, Ambra Sanmarco.

Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Internal Medicine–Piscaglia Unit, Bologna: Alessandro Granito, Luca Muratori, Fabio Piscaglia, Vito Sansone, Antonella Forgione.

Department of Surgical and Medical Sciences, Gastroenterology Unit, Alma Mater Studiorum–University of Bologna: Elton Dajti, Giovanni Marasco, Federico Ravaioli.

Department of Specialist, Diagnostic and Experimental Medicine, Radiology Unit, University of Bologna: Alberta Cappelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli.

Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital: Ester M. Cela, Antonio Facciorusso.

Department of Internal Medicine, Gastroenterology Unit, University of Genova, IRCCS Policlinico San Martino, Genova: Valentina Cacciato, Edoardo Casagrande, Alessandro Moscatelli, Gaia Pellegatta.

Gastroenterology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma: Nicoletta de Matthaeis.

Department of Gastroenterology, Polytechnic University of Marche, Ancona: Gloria Allegrini.

Gastroenterology Unit, Belcolle Hospital, Viterbo: Valentina Lauria, Giorgia Ghittoni, Giorgio Pelecca.

Vascular and Interventional Radiology Unit, Belcolle hospital, Viterbo: Fabrizio Chegai, Fabio Coratella, Mariano Ortenzi.

Department of Medicine and Surgery, Infectious Diseases and Hepatology Unit, University of Parma and Azienda Ospedaliero-Universitaria of Parma: Gabriele Missale, Andrea Olivani.

Gastroenterology Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar: Alessandro Inno, Fabiana Marchetti.

Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties, PROMISE, Gastroenterology & Hepatology Unit, University of Palermo: Anita Busacca, Giuseppe Cabibbo, Calogero Cammà, Vincenzo Di Martino, Giacomo E.M. Rizzo.

Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina: Maria Stella Franzè, Carlo Saitta.

Department of Medical, Surgical and Experimental Sciences, Azienda Ospedaliero-Universitaria of Sassari: Assunta Sauchella.

Department of Internal Medicine, Ospedale per gli Infermi di Faenza: Dante Berardinelli, Vittoria Bevilacqua, Alberto Borghi, Andrea Casadei Gardini, Fabio Conti, Anna Chiara Dall'Aglio, Giorgio Ercolani.

Department of Experimental and Clinical Medicine, Internal Medicine and Hepatology Unit, University of Firenze: Valentina Adotti, Umberto Arena, Chiara Di Bonaventura, Claudia Campani, Gabriele Dragoni, Stefano Gitto, Giacomo Laffi.

Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Napoli "Federico II": Pietro Coccoli, Antonio Malerba.

Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Napoli "Federico II": Maria Guarino, Maria Capasso.

Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa: Filippo Oliveri, Veronica Romagnoli.

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