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

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# Running head: How deprivation affects HCC mortality.

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**INTRODUCTION**

Studies on the impact of living conditions on health has a long history *[Bull World Health Organ. 2003; 81: 833–841;* [*Lancet.*](https://www.ncbi.nlm.nih.gov/pubmed/15781105) *2005;365:1099-104; Int J Epidemiol. 2017;46: 1312–1318.]*. Material deprivation measures poverty and takes into account not only financial resources but also the broader of aspects of living standards. It expresses the inability to afford some “basic” items, considered by most people to be desirable or even necessary, to lead an adequate life due to financial pressures and economic hardships. It represents a cause of social exclusion and is commonly employed to identify individuals whose material, cultural and social resources are so limited as to deny them full participation in their society. Deprivation represents one of most well-established health determinants. Differences in all-cause mortality as well as cancer survival between less and more deprived groups of individuals have been well-documented in different geographical areas worldwide *[J Clin Oncol. 1991;9:1500-9; Journal of Epidemiology and Community Health 1994;48:441-446; Eur J Public Health. 2016;26: 804–813.]*.

In the European Union (EU), liver cancer represents one of the five most common cancers and hepatocellular carcinoma (HCC) accounts for more than 80% thereof *[J Hepatol. 2018;69:182-236]*. Statistics from the UK Cancer Research Program clearly describe an association between liver cancer incidence and deprivation for males living in England. The *incidence* rate is 107% higher in males living in the most deprived areas compared with the less deprived ones. Similarly, there is evidence for an association between deprivation and liver cancer *mortality* for both males and females. Mortality rates are 100% higher for males and 72% higher for females in the most deprived areas compared with the least deprived *[https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk]*. Although these data indicate that deprivation affects both incidence and mortality from liver cancer, the underlying reasons have received little attention.

The main determinants of survival after HCC diagnosis are the stage at which the cancer is detected, accuracy of staging and optimization of available therapies *[J Hepatol. 2018;69:182-236; Hepatology. 2018;67:358-380; Nat Rev Gastroenterol Hepatol. 2010;7:448–458; Nat Rev Gastroenterol Hepatol. 2019;16:589-604]*. All these variables are inevitably influenced by the local resource levels. The World Gastroenterology Organization global guidelines on HCC defined high-resource countries as those where liver transplantation is available *[Nat Rev Gastroenterol Hepatol. 2010;7:448–458. Nat Rev Gastroenterol Hepatol. 2019;16:589-604]*. According to this definition, Italy represents a high-resource environment. Notwithstanding such definitions, it is pertinent to note that there are considerable economic and social inequalities across different Italian regions *[BMC Public Health. 2010 Jun 1;10:296. https://ec.europa.eu/eurostat/web/products-datasets/-/tgs00107]*. Such differences are likely to impact upon the pathway leading from prevention to early diagnosis and access to optimal treatment of HCC. Moreover, Italy is one of the EU countries burdened with the highest incidence of primary liver cancers *[J Hepatol. 2018;69:182-236]*.

The present study aims to examine, in a high resource country such as Italy, how material deprivation influences the stage of HCC at diagnosis, as well as the access to potentially curative treatments.

**METHODS**

**Study population**

Data collected in the Italian Liver Cancer (ITA.LI.CA) database was used for the present study. Since 1987, this registry has prospectively collected data on HCC patients diagnosed and treated in 23 centres across Italy. Data entry is updated every 2 years and is regularly checked for consistency by a dedicated coordinator. When clarification or additional information are deemed necessary, relevant cases are re-submitted to the recruitment centre before final inclusion in the database. The ITA.LI.CA database conforms to the current Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of personal data, and to the ethical guidelines of the Declaration of Helsinki.

From a total of 7705 registry entries (since 1987), 5196 patients diagnosed between January 2008 and December 2018 were selected for the present study. Of these, 867 patients lacked details regarding region of origin and 215 were still awaiting complete data entry leaving a total of 4114 for analysis.

**Diagnosis and treatment**

Surveillance for HCC of at-risk patients was offered to patients considered at-risk according to European and national guidelines released during the study period and was based on liver ultrasound, with or without α-fetoprotein (AFP) determination, performed every 6 (±1 month) or 12 months (±1 month). *[J Hepatol. 2008;48 Suppl 1:S20-37; Am J Gastroenterol. 2002 Mar;97(3):734-44;**Dig Liver Dis. 2013 Sep;45(9):712-23.]*

Diagnosis of HCC was based on the histology of 647 cases (15.7%). In the remaining cases, diagnosis was based on typical radiological features on one or more imaging techniques according to the international guidelines on HCC management *[J Hepatol. 2018;69:182-236; J Hepatol. 2008;48 Suppl 1:S20-37]*. Tumour number and size, major vascular invasion and patterns of metastatic spread were assessed by computed tomography (CT) or magnetic resonance (MR). The choice of therapy was mainly based on EASL guidelines, amended in the light of the individual patient’s circumstances and preferences, after review by a multidisciplinary team (MDT). These MDTs also took account of the local availability and/or accessibility of the various therapeutic options within their region. Consequently, the pattern of distribution of therapies across the participating centre was expected to be non-homogeneous *[Aliment Pharmacol Ther. 2016;43:814-24]*.

The therapeutic approach was hierarchically graded from the most to the least effective as follows: liver transplantation (LT), hepatic resection (HR), percutaneous ethanol injection (PEI), radiofrequency and microwave ablations (ABL), intra-arterial therapies (IAT), Sorafenib (SOR) and best supportive care (BSC). Transplantation, HR and ABL were defined as potentially curative treatments *[Liver Int. 2019;39:1478-1489]*.

**Material deprivation rate**

The material deprivation rate, as defined by the European Statistics on Income and Living Conditions (EU-SILC), reflects an individual’s ability to afford certain items widely considered desirable for an adequately fulfilled life *[https://ec.europa.eu/eurostat/web/products-datasets/product?code=tespm030]*. *Severe* material deprivation (SMD) rate is defined as the enforced inability to afford at least four of the following:

1. to pay their rent, mortgage or utility bills,
2. to keep their 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 European Union was 8.7%. The average percentage of individuals included in the present HCC study population (2008-2018) who fulfilled the SMD definition by Italian regions is reported in *Figure 1*. Each region was divided into three areas based on SMD tertiles - least deprived (Q1), intermediate deprived (Q2) and most deprived (Q3).

**Health Migrants definition**

Region of birth for each patient was matched with the corresponding SMD tertile by year of diagnosis. In Italy, the Italian National Statistics Institute (ISTAT) estimated an average inter-region migration (residence transfer) of 1.8%, over the entire Italian population between 2008 and 2018 *[https://www.istat.it/en/archivio/4050]*. Therefore, the region of birth was considered as a good proxy for the region of residence at the time of HCC diagnosis. For each hospital, the corresponding region was matched with the corresponding SMD tertile by year of diagnosis. Patients from regions with different levels of deprivation could stay in the original region or would have the option to move for HCC diagnosis and/or treatment to hospitals located in different deprived regions. Thus, heath migrants were defined as those patients travelling from the region of their residence to other regions to access different healthcare resources.

Yes, this is clear now

**Statistical analysis**

Missing data for clinical covariates were less than 10% and were estimated using the Maximum Likelihood Estimation method, as previously reported *[Liver Int. 2019;39:1478-1489]*. Differences for some categorical variables were evaluated using Pearson’s chi-square test, or through simple regression when searching for a relationship between variables and deprivation. In analysing probabilities of receiving surveillance or potentially curative therapies, a binomial regression (simple generalized linear model) was applied. Multinomial logistic regression was applied to investigate the effect of 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 using the methodology developed by Duffy et al. *[Am J Epidemiol. 2008;168:98-104; J Hepatol. 2014;61:333-41]*. Cox regression was applied to verify determinants of survival. For each regression applied, variables with p<0.10 at the univariate approach were included in the multivariable analysis.

**RESULTS**

**General characteristics**

Based on deprivation tertiles, 1350 patients (32.8%) belonged to the least deprived Italian regions, 1067 to the intermediate deprived regions (25.9%) and 1697 to the most deprived regions (41.3%). At the time of HCC diagnosis, the more deprived the region of origin the younger the patients were and the higher the percentage suffering from chronic hepatitis B or C (p<0.001). Conversely, the less deprived the region of origin the older the patients and more likely the aetiology was to be non-alcoholic steato-hepatitis (NASH) or alcoholic liver disease (p<0.001; *Table 1*). Notably, patients from the least deprived regions were more frequently diagnosed during the course of investigation for some other complaint (incidental diagnosis; p<0.001) than those from other regions, whereas patients from more deprived regions were more frequently diagnosed through surveillance (p<0.001). Symptomatic diagnosis was distributed similarly through the regions (p=0.128).

**Health migrants**

Most patients were diagnosed and treated in hospitals located within their local region. In fact, 93.6% of patients belonging to the least deprived regions were treated locally, but this proportion progressively decreased as the deprivation worsened, being 87.8% in the intermediate deprived regions and 61.4% in the most deprived regions (p<0.001). As a result, considering the whole patient population, 1716 patients (41.7%) were managed in hospitals located in the least deprived regions, 1319 were managed in hospitals of intermediate deprived regions (32.1%) and 1079 were managed in hospitals from the most deprived regions (26.2%).

**Tumour characteristics and survival by hospital regions**

Tumour features were similar among hospitals belonging to different regions (*Table 2*). Nevertheless, the more deprived the hospitals’ region, the lower the proportion of patients submitted to potentially curative therapies. Thus 56.9% received potentially curative therapy in hospitals located in the least deprived regions, compared to 51.6% and 50.3% for those of intermediate and most deprived regions respectively (p<0.001). Overall survival was better 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) (Table 2).

**Probability of being diagnosed during a surveillance program**

The likelihood of being diagnosed with HCC during surveillance (*Table 3*) was higher for females, for patients with MELD score ≤10, and for those bearing viral hepatitis regardless of patients’ regions (p<0.05 for these conditions in each region). Travel to less or more deprived regions did not affect the probability of being diagnosed during surveillance.

**Probability of receiving potentially curative therapies**

As expected, the adoption of potentially curative treatments (*Table 4*) mostly depended on MELD score, tumour burden, performance status and the presence of neoplastic vascular invasion, with a similar magnitude across different regions (p<0.05 for each variable in each region). However, multivariable analysis revealed that the migration from the most deprived regions toward less deprived regions, increased the probability of receiving potentially curative treatments by 1.11 times (relative risk; 95%C.I.: 1.03 – 1.19; p=0.006), independently from other features.

**Probability of receiving each type of therapy**

Details on the likelihood of receiving each therapy with migration, resulting from multivariable multinomial regression, are reported in the *Figure 2*. The migration of patients from the least deprived region toward more deprived regions returned a -6.8% probability of undergoing ABL (p=0.011) a +2.9% of receiving palliative therapies (p=0.041). Patients from the intermediate deprived regions had a 2.4% reduction of probability of receiving palliative therapies if they moved toward the least deprived regions (p=0.002). Patients who moved from the most deprived regions to the less deprived regions, increased their probabilities of LT of 2.5% (p=0.003) and of HR of 6.9% (p=0.007).

**Final impact on overall survival**

When survival was simply stratified by patients’ deprivation regions, no differences were observed between the three deprivation tertiles. Thus the median survival was 42 months (95%C.I.: 37.3 – 47.5) for patients belonging to the least deprived regions, 36.2 months (95%C.I.: 29.1 – 42.3) for the intermediate regions and 39.2 months (95%C.I.: 31.1 – 44.3) for patients from the most deprived regions (p=0.108).

Determinants of patient 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). Moreover, multivariable analysis revealed that, for patients belonging to the most deprived regions, the possibility of travelling to a less deprived regions increased survival probabilities, being the hazard ratio, adjusted for clinical determinants, of 0.78 (95%C.I.: 0.67 – 0.90; p=0.001).

**DISCUSSION**

The landmark study of Preston et al.in 1975, established the relationship between the national income and life expectancy *[Population Studies 1975;29(2):231-48]*. At the population-level this is to be expected as the protective effects of income are substantial. The present study which focused on HCC patients suggests, however, that there are other aspects to consider when evaluating how socio-economic status can affect health and outcome.

Italy is classified by the World Bank as a country with a “high-income economy” *[Country and Lending Groups. World Bank. Accessed on March 1, 2020.],* and with more than 20 LT centres fulfils requirements for being considered as having high resources for the treatment of HCC [*[Nat Rev Gastroenterol Hepatol. 2010;7:448–458. Nat Rev Gastroenterol Hepatol. 2019;16:589-604]*. However, it is important to note that Italy suffers from high income disparities. The European Statistical Office (Eurostat) currently places Italy’s income inequality ratio above the EU average and the most deprived Italian regions have SMD rates similar to those of lower-income countries such as Greece, Lithuania and Hungary *[https://ec.europa.eu/eurostat/web/products-datasets/product?code=tespm151]*. Our study confirms the relationship highlighted by the UK national statistics *[https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk]*. Overall survival figures are related to a worsening of deprivation when deprivation tertiles were identified by hospitals’ regions, but not by patients’ regions. These findings suggest that from the patients’ perspective, determinants of mortality for HCC are more complex than simply geographical origin, and that migration represents a backbone of them.

In our study, a large proportion of patients moved from more deprived regions to less deprived ones in search for better healthcare. This phenomenon was particularly evident for individuals from the most deprived areas, where it occurred in up to 40% of cases, so that it reversed the proportions between the patients’ origin region and hospital region.

In fact, most patients came from more deprived regions, but the hospitals of less deprived regions managed most individuals in need. This observation has important implications for the Italian national health system. Specifically, health migration toward hospitals located in the least deprived regions increased the chances of receiving potentially curative therapies by about 4-8% (corresponding to the RR of 1.11 of *Table 4*) and, even more importantly, increased the median survival by about 12 months (corresponding to an HR of 0.78, *Table 5*). Having identified such a large geographical variation across a high-income country such as Italy, we examined possible causes.

First, the chance of cure was not determined by access to *diagnostic* facilities. When stratified by patients’ region, HCC diagnosis was more frequently obtained during surveillance in patients living in more deprived regions, most likely due to the higher prevalence of chronic viral hepatitis, for which the guidelines indicate precisely when such patients should enter a surveillance program *[J Hepatol. 2008;48 Suppl 1:S20-37; Dig Liver Dis. 2013 Sep;45(9):712-23.].* When data were segregated by hospitals’ region deprivation, no differences were observed among tumor characteristics (*Table 2*) or diagnostic modality (*Table 3*).

The most striking observation is that the more deprived the hospitals’ region the lower the proportion of patients submitted to potentially curative therapies (*Tables 2 and 4*) and that migration from the most deprived regions toward hospitals located in the least deprived regions was associated with a higher chance of receiving such therapies. The exact opposite was observed when migration was directed from less deprived regions toward hospitals located in more deprived regions (*Table 4*).

Migration from the least deprived regions to more deprived regions decreased the probability (-6.8%) of being treated with ABL (*Figure 2*) which is mainly indicated for small tumors *[J Hepatol. 2018;69:182-236]*. It is possible that these small tumors were shifted to surgery (+5.1%) which is easier in small superficial lesions which would require a more demanding ablation approach *[Dig Surg. 2018;35(4):359-371.]*. The increase in costs would be minimal and affordable since only 6.4% of patients travelled to these regions. Alternatively, even if these patients had small tumors, they did not represent ideal surgical candidates and were consequently shifted to intra-arterial therapies (+5.7%).

The fact that patients who moved from the least to the more deprived regions had increased probabilities of receiving palliative therapies (+2.9%) should also be interpreted in the light of the opposite observation, that patients who travelled from the intermediate to the least deprived regions had decreased probabilities of receiving these therapies (-2.4%). This suggests that in the least deprived regions non-palliative therapies are more frequently adopted even for patients with advanced stages. These changes are very small. This paragraph isn’t very convincing and doesn’t add much to the discussion 🡪 I agree, do we remove it?.. **your decision but I would leave it out -PJ**

The most impactful finding was that patients who travelled from the most deprived to the less deprived regions had an increased probability of receiving either LT (+2.5%) and HR (+6.9%), whereas the ABL rate remained unaffected. It can be speculated that a different referral rate to a hepatic or transplant surgeon exists between less and most deprived regions or that different surgeons act differently among regions. That is, HCC patients which did not represent ideal candidates for HR or LT in they own regions may have migrated to less deprived regions which are able to sustain higher costs for these surgical procedures.

A large body of literature indicates that non-ideal candidates for HR can safely undergo this surgery, but also that surgery in these patients is demanding and requires additional preoperative evaluation of functional reserve. This may prolong the post-operative course, ultimately resulting in greater expense from the health-care providers’ perspective *[Ann Surg Oncol. 2020 Apr 9. doi: 10.1245/s10434-020-08444-3; J Hepatol. 2016 Jan;64(1):79-86.; Ann Surg. 2019 Jul 10. doi: 10.1097/SLA.0000000000003433].*

For LT the scenario is more complex. In Italy, there is a great variation in organ donation rate between the deprived regions (lowest) and less deprived regions (highest) *[http://www.trapianti.salute.gov.it/trapianti/archivioDatiCnt.jsp]*. Moreover, there are different graft allocation systems among different regions, so that donated organs are not distributed with a nationwide modality *[Am J Transplant. 2015 Oct;15(10):2552-61.].*

This will be an interesting research area for our next paper which will include the UK where there is nationwide sharing. 🡪 I need to think about it… let's talk about it at the next work

Consequently, the scarcity of donors adversely affects the actual feasibility of LT in centers located in the most deprived regions *[http://www.trapianti.salute.gov.it/trapianti/archivioDatiCnt.jsp]*, whereas LT centers located in less deprived regions can afford to transplant patients coming from other regions thanks to the more generous donation rate and the use of extended transplant criteria and down-staging procedures *[Am J Transplant. 2015 Oct;15(10):2552-61; J Hepatol. 2013 Mar;58(3):609-18.]*.. Of course, this policy is expensive and, considering that the proportion of migrants toward less deprived regions is consistent (38.6% in our study), it is affordable only in regions with higher per capita total health care expenditure.

The major limitation of the present study is the extent to which the populations studied are representative of the whole Italian HCC population and the sample size of some subgroups. Regarding the first problem, we compared our data with those provided by the Italian National Statistics Institute (ISTAT) for the period 2008 and 2018, by patients’ region of residence (thus, not by hospitals ICD registrations) *[hhtp://dati.istat.it; https://www.epicentro.iss.it/tumori/registri]*. In this period, the least deprived regions had a SMD index of 5.6% and the mortality for liver cancers was of 15.0/100.000 inhabitants. This figure is very similar to that seen in the most deprived regions, which was of 14.5/100.000 but in the presence of a SMD of 15.5%. Intermediate deprived regions had a mortality of 11.5/100.000 with a SMD of 7.2%.

It can be noted that there was no clear relationship between SMD worsening and mortality, by *patient* region. Thus, national data gives support to our results because the simple segregation of survival according to the deprivation tertile of patients’ region did produce clear differences. On the other hand, when our results were segregated by *hospital* region deprivation, there was a relation to mortality, as we observe is also reported in the UK statistics. It thus appears that the present results are likely to be representative of the majority of the HCC population diagnosed in our country. The second limitation of our study relates to the subgroup of patients who travelled from the least to the more deprived regions, which represents only 6.4% of the 1350 patients forming this tertile (86 patients). We acknowledge that data on treatment migration data reported in *Figure 2* should be treated with caution. You need to review this paragraph

In conclusion, the present study dissected the causes of mortality in a large cohort of HCC patients living in a high-resource environment area. A complex inter-relationship exists among etiology of liver disease, surveillance adoption and inter-regional travel in search of better health care. Migration of patients from the most deprived regions to hospitals located in less deprived areas resulted in a considerable increase in the adoption of potentially curative therapies and of surgical therapies, with the ultimate result of improved survival. These findings have significant implications for national health systems and measures/policies that might mitigate regional disparities.

**LEGENDS TO FIGURES**

**Figure 1.** Average distribution of the Severe Material Deprivation (SMD) ratio between different regions in Italy between 2008 and 2018. Based on SMD tertiles, three areas were identified as least deprived (Q1), intermediate deprived (Q2) and most deprived (Q3). The same region may have belonged to different deprivation tertiles between 2008 and 2018 (i.e. Abruzzo belonged to Q1 for one year (2012), belonged to Q2 for 7 years and to Q3 for 4 years.)

**Figure 2.** Results from multinomial logistic regression model showing that the probability of receiving a given treatment was modified by patient migration across different deprived regions.

**Table 1.** Some epidemiological and clinical characteristics of 4114 patients diagnosed with HCC between January 2008 and December 2018 by severe material deprivation tertiles.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Region of patients | | |  |
| Variables | Least deprived (n=1350) | Intermediate Deprived (n=1067) | Most Deprived (n=1697) | p-value\* |
| 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 |
| Etiology |  |  |  |  |
| 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** |
| 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 † | 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 |

\* P-value for linear trend

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

Abbreviations: MELD = model for end-stage liver disease.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Region of the hospital | | |  |
| Variables | Least deprived (n=1716) | Intermediate Deprived (n=1319) | Most Deprived (n=1079) | p-value\* |
| 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 |
| More than 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 | 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 [months, (median, 95%C.I.)] | 42.2 (38.2 – 46.9) | 38.3 (35.5 – 45.1) | 35.2 (31.2 – 41.2) | **0.008** |

\* P-value for linear trend

† survival was adjusted for lead-time bias for patients diagnosed through surveillance.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MaVI = macroscopic (neoplastic) vascular invasion.

**Table 3.** Probability (relative risk) of receiving potentially curative treatments for HCC in different material deprivation regions according to patients’ characteristics.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Region of patients | | |
| Variables | 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) † |
| Migrate to more deprived regions | 0.79 (0.61 – 1.02) | 0.98 (0.81 – 1.19) | - |
| Migrate to less deprived regions | - | 0.86 (0.52 – 1.39) | 0.96 (0.89 – 1.04) |

Numbers in parenthesis represent 95% confidence bands. Results derived from simple generalized 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.

Abbreviations: MELD = model for end-stage liver disease

\* <0.001

† <0.05

‡ <0.10

**Table 4.** Relative risk of receive potentially curative treatments according to different material deprivation regions and patients’ characteristics.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Region of patients | | |
| Variables | 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 | 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) \* |
| Migrate to more deprived regions | 0.86 (0.67 – 1.07) | 1.01 (0.84 – 1.23) | - |
| Migrate to less deprived regions | - | 0.98 (0.63 – 1.52) | 1.11 (1.03 – 1.19) † |

Numbers in parenthesis represent 95% confidence bands. Results derived from simple generalized 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.

Abbreviations: MELD = model for end-stage liver disease; ECOG = Eastern Cooperative Oncology Group; MaVI = macroscopic (neoplastic) vascular invasion.

\* <0.001

† <0.05

‡ <0.10

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | Region of patients | | |
| Variables | 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 | 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) \* |
| Migrate to more deprived regions | 1.13 (0.83 – 1.52) | 1.10 (0.84 – 1.44) | - |
| Migrate to less deprived regions | - | 0.82 (0.41 – 1.66) | 0.78 (0.67 – 0.90) † |

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.

Abbreviations: MELD = model for end-stage liver disease; ECOG = Eastern Cooperative Oncology Group; MaVI = macroscopic (neoplastic) vascular invasion.

\* <0.001

† <0.05

‡ <0.10

