Impact of Oral Immunonutrition on Postoperative Morbidity in Digestive Oncologic Surgery

A Nation-wide Cohort Study

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Objective: The objective of the present study was to assess the effect of preoperative immunonutrition on a nationwide scale.

Background: According to international guidelines, immunonutrition should be prescribed before major oncologic digestive surgery to decrease postoperative morbidity. Nevertheless, this practice remains controversial.

Methods: We used a prospective national health database named "Echantillon généraliste des Bénéficiaires." Patients were selected with ICD10 codes of cancer and digestive surgery procedures from 2012 to 2016. Two groups were identified: with reimbursement of immunonutrition 45 days before surgery (IN-group) or not (no-IN-group). Primary outcome was 90-day severe morbidity. Secondary outcomes were postoperative length of stay (LOS) and overall survival. Logistic regression and survival analysis adjusted with IPW method were performed.

Results: One thousand seven hundred seventy-one patients were included. The proportion of different cancers was as follows: 72% patients were included in the colorectal group, 14% in the hepato-pancreato-biliary group, and 12% in the upper gastrointestinal group. Patients from the IN-group (n = 606, 34%) were younger (67.1 ± 11.8 vs 69.2 ± 12.2 years, $P < 0.001$), with increased use of other oral nutritional supplements (49.5% vs 31.8%, $P < 0.001$) and had more digestive anastomoses (89.4% vs 83.0%, $P < 0.001$). There was no significant difference between the 2 groups for 90-day severe morbidity [odds ratio (OR): 0.91, 95% confidence interval (95% CI): 0.73–1.14] or in survival (hazard ratio: 0.89, 95% CI: 0.73–1.08). LOS were shorter in the IN-group [−1.26 days, 95% CI: −2.40 to −0.10)].

Conclusion: The preoperative use of immunonutrition before major oncologic digestive surgery was not associated with any significant difference in morbidity or mortality. However, the LOS was significantly shorter in the IN-group.

Keywords: digestive oncology, immunonutrition, morbimortality, surgery

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Nutritional status of patients is an important issue in oncologic therapy. Cancer is often associated with malnutrition. Inadequate nutritional intake (mostly in digestive cancer), muscle protein depletion, and systemic inflammation syndrome are involved in the poor nutritional status in oncologic disease.[1] The management of malnutrition is now included in the recommendation of enhanced recovery after surgery (ERAS) and implies the use of immunonutrition before surgery.[2]

The evidence supporting the systematic use of immunonutrition in major digestive oncologic surgery relies on some randomized controlled trials (RCTs)[3–7] and meta-analyses,[8–10] which show a decrease in overall postoperative complications rate, in particular for infections and a decrease in the hospital length of stay (LOS). International guidelines,[11] established by the European Society for Clinical Nutrition and Metabolism, recommend that immunonutrition should be given to malnourished and high-risk patients 7 days before major oncologic surgery. The use of preoperative immunonutrition has been recommended for all patients before oncologic surgery in France since 2005.[12]

These guidelines are justified by the composition of this particular nutritional formula. Immunonutrition contains immune-modulating agents such as arginine, n-3 fatty acids, and RNA from yeast extracts. The use of arginine is based on immune modulatory actions[13] and inflammatory modulation. N-3 fatty acids also modulate the inflammatory response.[14] Nucleotides and RNA supplementation likely avoid the decrease in T-lymphocytes and interleukin-2 synthesis.[15,16]

Despite the introduction of immunonutrition in the national guidelines for oncologic surgery, its use remains controversial. In fact, the original RCTs regarding immunonutrition have been criticized for their relatively small sample size[3,17–19] and potential conflict of interest.[3–5,20]

More recently, 2 studies have reported results that show a considerably lower effect of preoperative immunonutrition on surgical outcomes. Thornblade et al[21] found no significant difference in serious adverse events in a large retrospective study. They matched a prospective cohort of 960 patients in the Washington State on a propensity score based on the probability of receiving immunonutrition and analyzed severe complications and LOS. Only LOS was significantly reduced in the immunonutrition group. Probst et al[20] in a meta-analysis related a positive global effect but no advantage on

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overall complications after exclusion of studies with bias, including more than 2000 patients from 19 studies. The same result was found after the exclusion of industry-funded studies (6 studies, 1142 patients). They also pointed out a potential publication bias concerning the infectious complications.

Immunonutrition is reimbursed in France by the national health system, and all data regarding drug reimbursement are recorded in the national health database. The main objective of this study was to assess the effect of immunonutrition on 90-day morbidity, survival, and LOS following surgery for digestive cancer.

METHODS

Study Design, Settings, and Participants

This study is a cohort study using a 1% sample of the national administrative database Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM), which is the French Statutory healthcare insurance system database covering a population of approximately 66 million affiliates,[22,23] that is, more than 98.8% of the French population. Seven hundred and eighty thousand patients are in the database. The selection of patient in the database is randomly done by picking 1 number out of 97 of the sum of their health care number.[24] This database called ''Echantillon Généraliste des Bénéficiaires'' contains all outpatient reimbursed health expenditures, data on hospital stays, and an all-cause national death registry. Hence, any outpatient drug reimbursement can be identified though a specific coding, which permits identification of the type of drug, and the date of delivery. The ''Echantillon généraliste des bénéficiaires'' is tested to be representative of the national population for age, sex, occupation, and medical reimbursement.[24]

Data on hospital stays are provided by all French private or general hospitals. Information includes the hospital identifier, the dates of start and end of stays, diagnostic codes, diagnosis-related group codes, and a national procedures classification [*Classification Commune des Actes Médicaux* (CCAM)], which describes surgical endoscopic and radiological procedures.

From the January 1, 2012, up to the December 31, 2016, patients were identified by cross matching the ICD10 codes for cancers (appendix 1, http://links.lww.com/SLA/B620) with the codes of oncologic digestive resections (appendix 2, http://links.lww.com/SLA/B620). The immunonutrition group was constituted after identifying reimbursement of immunonutrition prescribed under the name Oral Impact with the code 1190280, within 45 days before surgery. This product was selected because national guidelines advocate oral impact for preoperative use in major oncologic abdominal surgery and it is the only reimbursed oral immunonutrition in France. Patients who had no reimbursement, or if the date of reimbursement was not available were included in the control group.

Patients less than 18 years of age, with a second hospital stay for oncologic digestive surgery, or operated in emergency were excluded. An unknown primary oncologic site defined by the ICD10 code C78 was excluded from the subgroup analysis.

Covariates

Demographic characteristics were age, sex, location of cancer, type of hospital (academic, public, or private), and universal medical coverage as a marker of supplementary healthcare coverage named *Couverture Maladie Universelle Complémentaire*.

The Charlson comorbidity[25] index according to the version reported by Bannay et al[26] was constructed for each patient. Medical history of obstructive sleep apnea syndrome (OSAS), inflammatory bowel disease (IBD), obesity with a body mass index higher than 30 kg/m^2, or malnutrition was constructed by identifying the ICD10 code (appendix 3, http://links.lww.com/SLA/B620). These covariates were separately analyzed because they were not present in the Charlson index. The use of other standard oral nutritional supplements (ONS) in the last 3 months before surgery was identified by codes summarized in appendix 4, http://links.lww.com/SLA/B620. Surgical information concerning the surgical approach, the type of resection, the presence of an anastomosis, and the year of surgery were collected using the CCAM codes (appendix 2, http://links.lww.com/SLA/B620). The types of cancer locations were defined as follows: upper gastrointestinal (upperGI) for esophageal, gastric, and small bowel cancers, colorectal for colonic, rectal, and anal cancers, and hepato-pancreato-biliary (HPB) tract for gallbladder, biliary tract, hepatic, or pancreatic cancers.

Outcomes

The primary outcome was severe morbidity at 90 days after surgery defined by the occurrence of a complication during the first hospital stay irrespective of the length or within the 90 postoperative days after the first discharge. We defined severe complications as Clavien-Dindo classification,[27] including grade III, IV, and V. The grade IIIa was defined as a réintervention at least 1 day after primary surgery (appendix 2 and 5, http://links.lww.com/SLA/B620). The grade IIIb was defined by the occurrence of a grade IIIa complication under general anesthesia. The grade IV was at least 2 days of hospitalization in intensive care unit (ICU). We also studied all infectious complications, including pneumonia, urinary infections, and wound infections and other noninfectious complications as liver failure, bleeding, respiratory failure, and renal failure (appendix 6, http://links.lww.com/SLA/B620).

Secondary outcomes were mortality and LOS. Death was recorded until March 2018. Death and the LOS were analyzed as continuous and as binary variables. Ninety-day mortality was defined by death within the 90 postoperative days. A variable, long LOS, was constructed using the third quartile of length[21] for each type of surgery (16 days for colorectal surgery, 23 days for HPB surgery, and above 25 days for upperGI surgery). Data measurement was done prospectively in each center as routine practice of coding.

Data Management and Bias

Data extraction was performed by 2 different authors (AC and DD) to reduce potential bias. A list of variables to identify all confounders was created in multidisciplinary meetings. Charlson score and age were used as quantitative variables.

Type of Analysis

Analyses were done with R software (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are expressed as percentages for categorical variables, and means and standard deviations for continuous data. In univariate analysis, general linear models were used to compare variables.

A propensity score was built by logistic regression on several confounders and covariates associated with the outcomes previously selected[28]: age, sex, Charlson index, medical history of OSAS, IBD, chemotherapy, radiotherapy, malnutrition, obesity, surgical approach, localization of cancer, multiple resections, presence of anastomosis and/or stoma, the use of other ONSs, universal medical coverage, and time (reported as quarter of year). We used the inverse probability of treatment-weighting methods on propensity score to adjust the analysis.[29] Analysis was done using fit general linear models for binary outcomes and fit linear models for continuous outcomes. Survival analysis was also done after adjustment with adjusted Kaplan-Meier curves, and adjusted a Cox proportional hazards regression model. Results of the adjustment analysis were presented with odds ratios (ORs) and 95% confidence intervals (95% CIs) for binary outcomes, as coefficients for continuous outcomes,

and as hazard ratios (HRs) for survival. A subgroup analysis was done by type of cancer with the initial adjustment. Results were reported according to the RECORD guidelines.[30]

RESULTS

Participants

A total of 1771 patients were included in the final dataset (Fig. 1). A subgroup analysis was performed according to the type of cancer; 72% (n = 1279) patients were included in the colorectal group, 14% (n = 256) in the HPB group, and 12% (n = 218) in the upperGI group. Mean age of patients was 68.5 ± 12.1 years at surgery and 41% (n = 733) were female; 15% (n = 265) were obese and 25% (n = 443) were malnourished. After patient selection, patients were scattered across 521 different hospital centers.

Descriptive Data

Baseline characteristics of the 2 groups are presented in Table 1. The immunonutrition group (IN) represents 34% (n = 606) of the patients versus 66% (n = 1165) of the patients in the no immunonutrition group (no-IN). There were significant differences in age (IN: 67.1 ± 11.8 vs no-IN: 69.2 ± 12.2 years, $P < 0.001$), OSAS (IN: 6.8% vs no-IN: 3.9%, $P = 0.01$), history of chemotherapy (IN: 20.0% vs no-IN: 14.2%, $P = 0.002$) or radiotherapy (IN: 16.8% vs no-IN: 10.6%, $P < 0.001$), and in the use of other ONSs in the last 3 months (IN: 49.5% vs no-IN: 31.8%, $P < 0.001$).

Surgical characteristics of the patients are all summarized in appendix 7, http://links.lww.com/SLA/B620. The global rate of open surgery was 65.5% not different in groups. Digestive anastomoses were significantly more frequent in the immunonutrition group (IN: 89.4% vs no-IN: 83.0%, $P < 0.001$). Proportion of immunonutrition use increased by year ($P < 0.001$) (appendix 8, http://links.lww.com/SLA/B620): from 2012 to 2016, the number of prescriptions before major surgery increased from 23% to 42%. After adjustment, no differences were found in the study population as shown in appendix 9, http://links.lww.com/SLA/B620.

Severe Morbidity Rate at 90 Postoperative Days

We reported 58% (n = 1026) of patients with complications and 20% (n = 352) with severe complications. Details of the complications are provided in Table 2. In univariate analysis, no significant differences were found between groups for overall 90-day severe morbidity (OR: 0.86, 95% CI: 0.67–1.10) or for specific complications reported as infectious and noninfectious. After adjustment (Table 3), the severe morbidity rate remained not significant (OR: 0.91, 95% CI: 0.73–1.14) for the entire population and for the different subgroups (Table 4).

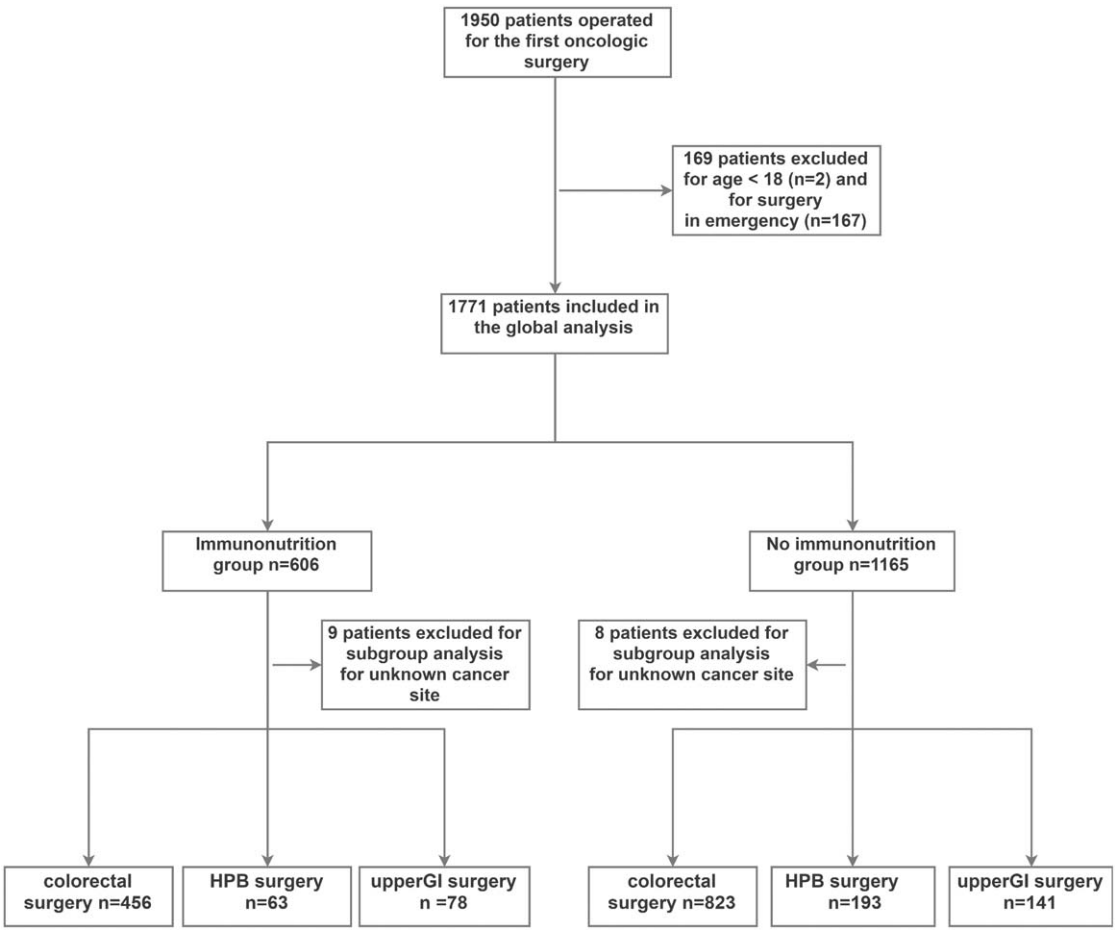

FIGURE 1. Flow chart of the study with the oncologic digestive-operated population from 2012 to 2016. HPB indicates hepato-pancreato-biliary; upperGI, upper gastrointestinal.

TABLE 1. Baseline Characteristics of the Population by Treatment Group from 2012 to 2016 (n = 1771)

	Immunonutrition (n = 606)	No Immunonutrition (n = 1165)	*P*
Age in y, mean (sd)	67.1 ± 11.8	69.2 ± 12.2	<0.001
Female	39.1, (n = 237)	42.6, (n = 496)	0.18
Charlson score, m (sd)	6.0 ± 5.2	6.3 ± 5.4	0.3
OSAS	6.8, (n = 41)	3.9, (n = 46)	0.01
IBD	1.8, (n = 11)	1.3, (n = 15)	0.5
History of radiotherapy	16.8, (n = 102)	10.6, (n = 123)	<0.001
History of chemotherapy	20.0, (n = 121)	14.2, (n = 165)	0.002
Obesity	14.4, (n = 87)	15.3, (n = 178)	0.66
Malnutrition	25.9, (n = 157)	24.5, (n = 286)	0.57
Other nutritional complements in the last 3 mo	49.5, (n = 300)	31.8, (n = 370)	<0.001
Universal medical coverage	10.2, (n = 62)	10.8, (n = 126)	0.77
Type of hospital			
Public academic	24.8, (n = 150)	24.8, (n = 289)	0.05
Public nonacademic	47.4, (n = 287)	52.4, (n = 610)	
Private	27.9, (n = 169)	22.8, (n = 266)	
Surgical characteristics			
Open surgery	65.2, (n = 395)	65.7, (n = 765)	0.88
Digestive anastomosis creation	89.4, (n = 542)	83.0, (n = 967)	<0.001
Stoma creation	23.4, (n = 142)	19.7, (n = 230)	0.08

Data are % unless specified.
IBD indicates inflammatory bowel disease; OSAS, obstructive sleep apnea syndrome.

Survival

Survival analysis did not outline a difference after a mean follow-up of 33 ± 20 months (Fig. 2) (HR: 0.89, 95% CI: 0.73–1.08). After categorization, immunonutrition was not associated with 90-day mortality (OR: 0.79, 95% CI: 0.46–1.35).

TABLE 2. Proportion of 90-day Morbidity by Treatment Group from 2012 to 2016 (n = 1771)

Outcome	Immunonutrition (n = 606)	No Immunonutrition (n = 1165)	*P*
Severe complications at 90 POD	18.3, (n = 111)	20.7, (n = 241)	0.26
Grade IIIa	4.5, (n = 27)	4.5 (n = 52)	
Grade IIIb	2.0, (n = 12)	2.3, (n = 27)	
Grade IV	4.0, (n = 24)	4.3, (n = 50)	
Grade V	3.5 (n = 21)	6.7 (n = 78)	
Morbidity at 90 POD	56.8, (n = 344)	58.5, (n = 682)	0.5
Infectious complications	46.9, (n = 284)	45.4, (n = 529)	0.59
Peritonitis	9.1, (n = 55)	9.4, (n = 109)	
Leakage	14.5, (n = 88)	14.6, (n = 170)	
Abdominal abscess	19.3, (n = 117)	15.3, (n = 178)	
Pneumonia	12.7, (n = 77)	14.2, (n = 166)	
Urinary tract infection	17.5, (n = 106)	19.1, (n = 222)	
Wound infection	7.1, (n = 43)	6.4, (n = 74)	
Noninfectious complications	32.3, (n = 196)	36.1, (n = 421)	0.12
Liver failure	3.0, (n = 18)	2.0, (n = 23)	
Intestinal infarction	3.6, (n = 22)	2.7, (n = 31)	
Bleeding	8.1, (n = 49)	10.6, (n = 123)	
Shock	7.8, (n = 47)	8.8, (n = 102)	
Thromboembolic disease	9.7, (n = 59)	9.5, (n = 111)	
Respiratory failure	9.7, (n = 59)	9.3, (n = 108)	
Renal failure	10.7, (n = 65)	12.4, (n = 145)	
LOS mean ± sd	14.6 ± 12.8	15.9 ± 12.0	0.03
Long LOS	21.1, (n = 128)	25.3, (n = 295)	0.06

LOS indicates length of stay; POD, postoperative days.
Data are % (n) unless specified.

Length of Stay

LOS was significantly lower in the immunonutrition group with a coefficient of −1.26 days (95% CI: −2.4 to −0.1) after adjustment. Long LOS hospitalizations were less common in the immunonutrition group (OR: 0.80, 95% CI: 0.65–0.98). After subgroup analysis, long LOS was lower in the colorectal group (OR: 0.73, 95% CI: 0.57–0.93) but was nonsignificant in the other subgroups.

DISCUSSION

In this large national cohort study, no difference was found between the preoperative immunonutrition and no preoperative immunonutrition groups in terms of severe complications or 90-day morbidity or 90-day mortality. In the subgroup analysis, no difference was found for infectious or noninfectious complications. There was, however, a decrease in the LOS in the immunonutrition group, compared with the control group.

Guidelines for the use of immunonutrition are based on a decrease in the rate of infectious complications.[2,3,18–22] Braga et al[31] was one of the first studies to describe a positive effect of immunonutrition in a RCT. Infectious morbidity was divided by 2 with perioperative immunonutrition. The same team[32] studied the

TABLE 3. Primary and Secondary Outcomes Analyses in Univariate and Inverse Probability Weighting (IPW) Propensity Adjustment by Treatment Group from 2012 to 2016 (n = 1771)

Outcome	Univariate Analysis	95% CI	IPW Analysis	95% CI
Severe 90-day morbidity	0.86	0.67–1.10	0.91	0.73–1.14
90-day morbidity	0.93	0.76–1.13	0.97	0.89–1.06
Infectious complications	1.06	0.87–1.29	1.02	0.91–1.15
Noninfectious complications	0.84	0.69–1.04	0.90	0.78–1.05
Long LOS	0.79	0.62–1.00	0.80	0.65–0.98
LOS (coefficient in days)	−1.31	−2.50 to −0.10	−1.26	−2.40 to −0.10

Data are presented as odds ratios unless specified.
LOS indicates length of stay.

TABLE 4. Subgroup Analyses for Primary and Secondary Outcomes in Univariate and IPW Propensity Adjustment by Treatment Group from 2012 to 2016 (n = 1748)

Type of Surgery	Outcome	Univariate OR	95% CI	OR After Weighting	95% CI
Colorectal surgery	90-day severe morbidity	0.79	0.57–1.10	0.79	0.59–1.06
	90-day morbidity	0.88	0.70–1.11	0.93	0.83–1.04
	Infectious complications	1.01	0.80–1.27	0.98	0.85–1.13
	Noninfectious complications	0.82	0.64–1.05	0.87	0.72–1.05
	Long LOS	0.70	0.53–0.92	0.73	0.57–0.92
	LOS (coefficient in days)	−2.09	−3.20 to −0.90	−2.24	−3.30 to −1.10
HPB surgery	90-day severe morbidity	0.65	0.32–1.24	0.85	0.48–1.49
	90-day morbidity	1.10	0.60–2.06	1.02	0.83–1.25
	Infectious complications	1.29	0.73–2.29	1.12	0.83–1.5
	Noninfectious complications	0.74	0.41–1.31	0.82	0.56–1.21
	Long LOS	1.28	0.66–2.40	0.97	0.56–1.68
	LOS (coefficient in days)	2.89	−1.40 to 7.23	1.97	−1.90 to 5.83
UpperGI surgery	90-day severe morbidity	1.64	0.92–2.93	1.38	0.94–2.03
	90-day morbidity	1.21	0.69–2.16	1.12	0.90–1.39
	Infectious complications	1.17	0.67–2.05	1.12	0.87–1.46
	Noninfectious complications	1.35	0.77–2.37	1.19	0.84–1.69
	Long LOS	1.04	0.55–1.96	1.01	0.60–1.69
	LOS (coefficient in days)	1.03	−4.00 to 6.13	0.01	−5.00 to 5.03

LOS indicates length of stay.

preoperative use of immunonutrition and found the same results with a global morbidity rate near 40%. In this study, the association between immunonutrition and the rate of infections was not so evident. In fact, we showed no difference for this specific outcome with a greater rate of infection in the immunonutrition group and an OR of 1 after adjustment. Our global morbidity rate was higher than the last study, although the follow-up was longer, and the inclusion criteria were less selective. Similar findings were reported by other authors[17,20,33–37] in different subtypes of surgery. Giger-Pabst et al[35] and Nakamura et al[38] demonstrated only a biological effect on

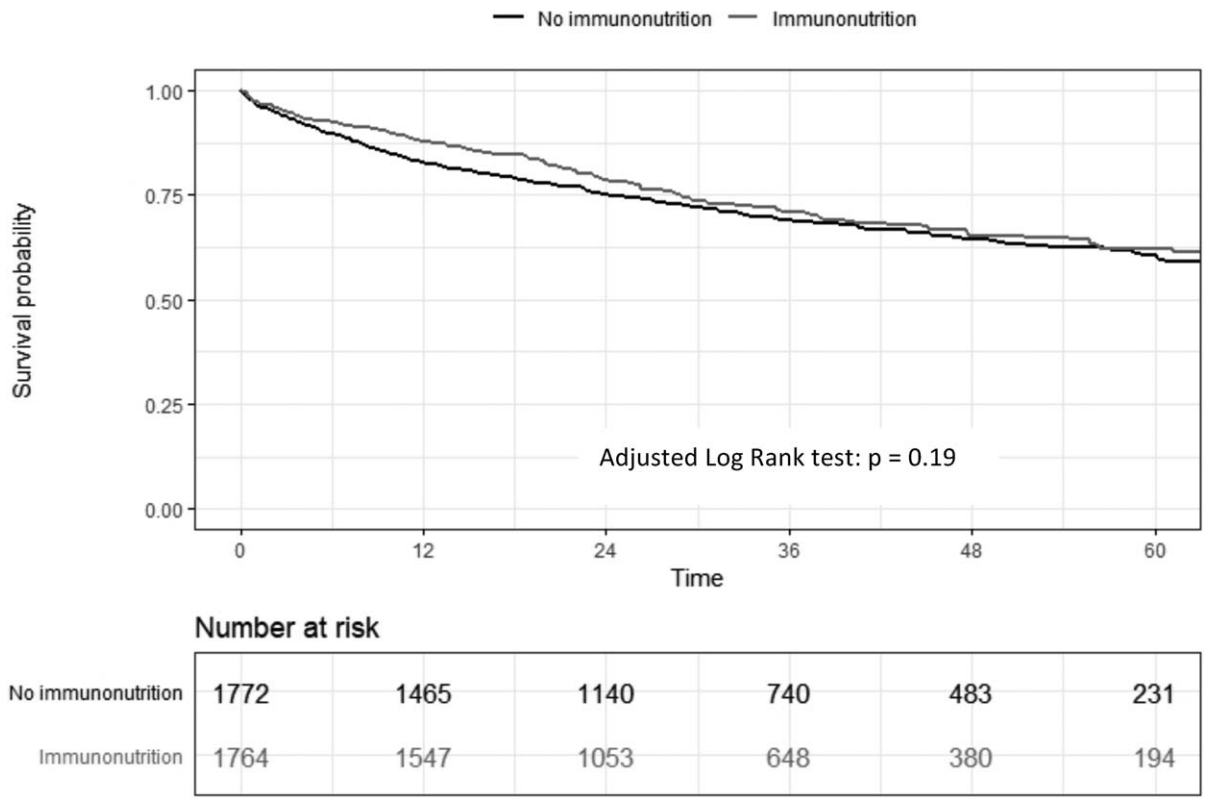

FIGURE 2. Adjusted Kaplan-Meier curves for survival with or without immunonutrition.

C-reactive protein levels in the postoperative course at 7 postoperative days but not on overall morbidity. Interestingly, a recent meta-analysis[20] related a positive effect of immunonutrition on morbidity. Nevertheless, after the exclusion of high-risk bias trials, the effect on overall morbidity was no longer significant. Furthermore, they showed no effect on any outcome after exclusion of industry-funded studies, as well as for infectious complications. They showed that the outcome infectious complications were significantly affected by publication bias. The authors concluded that the existence of bias lowers the confidence in the existing evidence. In this background of several funded trials, a retrospective analysis of a large national prospective cohort was appropriate to study the potential effect of immunonutrition in oncologic digestive surgery. Furthermore, a study[39] found an association between industry-funded trials and to report a positive outcome in a large meta-analysis done in general and abdominal surgery.

In this study, preoperative immunonutrition was not associated significantly with any differences in survival or 90-day mortality. This is consistent with the recent meta-analysis[20] and several other studies.[1,3,6,22,23,26]

However, consistent with previous studies, we showed an association between preoperative immunonutrition and LOS after propensity score weighting and subgroup analysis in the colorectal group. Nevertheless, a recent study[21] showed a reduction of long LOS after colorectal surgery. This result should be analyzed with caution. First, the characteristics for discharge were not standardized, as the retrospective use of administrative database does not allow us to control for it. But as this database is representative of an entire country, we think the limit will not constitute a bias. Second, the reduction of LOS could be associated with a progressive development of ERAS, which includes immunonutrition in their guidelines, which is non measurable in our database. Effective ERAS protocol provides a reduction of LOS by nearly 2 days according to Greco et al.[40] However, ERAS protocol decreases postoperative morbidity, so our results do not highlight imbalance in favor of immunonutrition group. Third, one of the explanations could be the surgical approach, but the rate of minimally invasive surgery was the same in the 2 groups and was one of adjustment variable.

The main strength of our study is the large sample size with one of the longest follow-up ever studied with the assessment of surgical morbidity at 90 postoperative days and a long-term mortality analysis. The inclusion of all digestive cancers provides the possibility of addressing the impact of immunonutrition in specific areas, for example, colorectal surgery.

Our study presents several limitations. First, health care databases could present a measurement bias because administrative data are recorded for billing purposes and not for scientific research, which could lead to overcoding or undercoding depending on the financial value of the code. Complications were not defined before the beginning of the study and it could also affect the measurement of outcomes. In light of this bias, we decided to study a composite outcome including only severe complications to avoid assessment error. We believe that this bias stays minimal regarding the high number of centers composing this cohort. The lack of information concerning ''non-hospitalized'' follow-up could underestimate the morbidity. Nevertheless, this effect likely affects the 2 groups similarly. Second, we are unable to measure the adherence of patients to the use of immunonutrition; we only can assess the reimbursement of the treatment. However, the out-hospital compliance to a treatment is the same as in a RCT. We are unable to determine the use of immunonutrition during the postoperative periods leading to ignore a potential effect of postoperative use in the no immunonutrition group or overestimate the treatment effect in the immunonutrition group. However, there is no national guideline suggesting the use of immunonutrition postoperatively, so it is likely an overestimation of the treatment effect in the immunonutrition group. Third, several confounders may not have been measured: as a center effect.

In conclusion, the use of immunonutrition was not associated with a reduced 90-day morbidity, reduced infectious or noninfectious complications, or mortality rate. Immunonutrition was associated with a shorter LOS. These results challenge the clinical utility of systematic immunonutrition in the preoperative period of major digestive oncologic surgery.

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