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The use of administrative data for the evaluation of healthcare interventions in chronic disease related to HCV

CIAMPICHINI ROBERTA

Registration number 078850

Tutor: Prof. Giancarlo Cesana

Co-tutor: Ass. Prof. Lorenzo Giovanni Mantovani

Coordinator: Prof. Giancarlo Cesana

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1. Introduction

Public Health and Health Technology Assessment

The present document describes the results of a project developed through the PhD on Health Technology Assessment (HTA) in Public Health.

Sir Don Acheson in 1988 defined the Public Health as "the art and science of preventing disease, prolonging life and promoting health through the organized efforts of society" [1].

In order to perform their work the policy decision makers engaged in Public Health could use the information coming from HTA outcomes. Indeed HTA is a form of policy research in which short- and long-term effects of health care thechnology[1] are studied in a systematic and multidisciplinary way. HTA studies the medical, social, ethical, and economic implications of the development, diffusion and use of health technology [2].

Decision-analytical models within HTA framework and Markov Models

One important tool in HTA is represented by decision-analytical (DA) models that synthetize the evidence on the outcomes and costs of alternative healthcare interventions.

The Markov models [3], a particular type of DA models, are frequently used in medical-decision making, since they express the consequences of healthcare interventions involving both resources and health outcomes. The Markov models are particularly suited to modelling the progression of chronic disease, which is represented by 3 elements: mutually exclusive disease states, transition probabilities between these states over a discrete time periods (Markov cycles).

Under specific intervention condition (e.g. treatment, no treatment), each disease state is associated to weights indicating the life expectancy in that state (weight equals to 0 for death state and 1 elsewhere), the quality of life experienced in that state (weight between

[1] Health (care) technologies are the drugs, devices, procedures and the organizational and support systems in the field of health care

0 and 1, e.g. EQ-5D utility score), and the costs of staying in that state. These weights allow the model to predict life expectancy, life expectancy adjusted for quality of life (QALY) and costs in the process.

The model is usually run on a hypothetical cohort beginning the process with some distribution among the disease states (e.g. 70% of the cohort starts from “HCV infected” stated, 25% from “Cirrhosis” and 5% from “Decompensated Cirrhosis” or 100% from “HCV infected”). The running of the model starts: for each cycle the cohort is distributed among the disease states according to the transition probabilities resulting in a new distribution of the hypothetical cohort among the disease states.

The life expectancy accrued for the cycle is given by the sum of the times spent in the states to arrive at an expected survival for the process. Summing the life expectancy across all cycles of the model and dividing it by the number of the cohort give the life expectancy per patient.

The life expectancy adjusted by the quality of life accrued for the cycle is given by the sum of the weights (from 0 to 1) multiplied by the fraction of the cohort in all the states.

Summing the adjusted life expectancy across all cycles and dividing it by the number of the cohort give the QALY per patient.

The cost spent in the cycle is given by the sum of the costs multiplied by the fraction of the cohort in all the states. Summing the cycle cost across all cycles of the model and dividing it by the number of the cohort give the average cost per patient.

Once the run ends the model gives the estimation of the incremental cost-effectiveness ratio, given by the ratio (ICER) between incremental cost and incremental effectiveness of the two treatment options. There is no official willingness-to-pay threshold in Italy to discuss the cost-effectiveness of a treatment and researchers usually do 40,000€ per QALY gained [4,5].

Chronic Liver Disease caused by HCV infection

According to the Lombardia Hepatitis Network in 2014 the number of CHC patients followed for their disease was around 37,600, 42% of them classified as having advanced

fibrosis or cirrhosis. The main liver centers across the region are located in Milano, Bergamo and Brescia [6]. Just few years ago the standard of treatment for the chronic hepatitis C (CHC) was the combination therapy with pegylated interferon alpha (PEG-IFNα) and ribavirin (RBV) [7]. “Treatment is lengthy and has severe side effects, which may lead to dose reduction or even prevent treatment completion. There are also several contraindications to starting treatment, such as ongoing psychiatric disease or active intravenous drug use” [8]. A new treatment for CHC infection, also known as direct-acting anti-virals (DAAs), is now available. It has an excellent safety profile and few drug interactions making possible to treat and cure a higher number of patients with respect to the old treatment [9]. On the other hand its relative high price and the prevalence of the disease have generated the need of economic evaluations for many health care systems: these new treatments may become restricted to certain categories of patients. Several studies on the cost-effectiveness comparison between the standard care and the new ones have been performed using the Markov model approach. Moreover another issue is becoming important in CHC management: the increasing prevalence of CHC among elderly patients. This prevalence varies between 2-13% among people over 65 years old compared with less than 2% in the general population [10]. A recent meta-analysis [11] showed a pooled estimation of HCV infection prevalence among older adults in long-term care settings equal to 3.3 (95% CI: 1.5-7.2%). The increasing trend is expected to further increase: people born between 1945-1965 is believed to have become infected when the virus was unknown and consequently universal precautions and infections control procedures were not adopted. Along with the relatively high number of elderly patients to treat, the healthcare service has to consider their potential more severe liver condition and ineligibility to (IFN)-based treatments [4, 5].

Markov model for cost-effectiveness of DAAs

Markov models developed in this field took their data from available national and international studies and reviews. These results are often related to a reality different from the one we are interested to (in example data from Japain studies used to perform economic evaluation for the Italian healthcare setting) or, more generally, are related to a population different from the one we want to investigate on (in example data from young

patients used to perform evaluation for the older ones). In those cases the use of administrative data could be usefull, expecially in the Italian Healthcare Service, that has a universal coverage funded by tax, representing the 93% of the total healthcare expenditure (7% is represented by private assurance in charge of patients).

Objectives of the present work

The objective of the present work is **threefold**.

First, we want to describe the burden of chronic hepatitis C (CHC) by phase of disease using a population (study population) selected from administrative healthcare data. We want to express that burden in terms of incidence, prevalence, mortality and direct healthcare costs.

Second, we want to discuss on the use of administrative data to perform economic evaluation by Markov models. Using the CHC study population we want to populate a validated Markov model [4] and make discussion on results.

Third, we want to focus on the use of administrative data in order to fill missing informations, as those related to elderly CHC patients. Using the study population obtained from the first aim we want to populate a validated Markov model [5] and make discussion on results.

In order to reach the **first** aim, we perfomed the following steps:

1. We defined a selection algorithm to detect a population of subjects recognized as having CHC by the local healthcare service (LHS) of the Province of Bergamo (paragraph 2.1);
2. We described the methods to estimate the burden of disease associate to the study population (paragraph 2.2);
3. We described the methods to estimate the transition probabilities among states and mean cost per patient per year in that state (paragraph 2.2).

In order to reach the **second** aim, we perfomed the following steps:

1. We slighlty modify the Markov model developed by Cortesi et al [4] in order to make it suitable to our data and aims (paragraph 2.3);

2. We populated the Markov model for young patients using the parameters estimated from the not treated study population aged 15-64 (paragraphs 3.5, 3.6);
3. We then compared the Cortesi et al [4] deterministic results with the ones obtained by LHS data (paragraph 4).

In order to reach the **third** aim, we perfomed the following steps:

1. We slighlty modify the Markov models developed by Ciaccio et al [5] in order to understand if the new interferon-free treatment was cost-effectiveness on patients older than 65 (paragraph 2.4);
2. We populated the Markov model for elderly using the parameters estimated from the not treated study population aged over 65 (paragraphs 3.5, 3.6);
4. We then compared the Ciaccio et al [5] deterministic results with the ones obtained by LHS data (paragraph 4).

2. Materials and methods

2.1 The source and the study populations

We defined the study population from administrative data and observe them from the moment in which they were defined as patients with CHC from the health care service until the end of observation, passing through potential disease progression. From the study population we will estimate the parameters required by the two Markov models used to perform the cost-effectiveness analysis of DAAs versus no treatment.

2.2 The source population

The source population was given by subjects resident in the Province of Bergamo, one of the provinces in which the Italian Lombardy Region is organized in. The heatlh care service for those subjects are covered by the Local Health Service (LHS) of Province of Bergamo. The health care administrative archives available from the LHS and used in the present study were referred to the period 2000-2014 and were: demographic characteristics (gender, date of birth, date of death), hospital discharges (HDs, containing diagnosis and procedures both coded by ICD-9-CM), pharmaceutical prescriptions (coded by the Anatomical Therapeutic Chemical Classification System - ATC), outpatient claims (laboratory and diagnostic examinations, specialist medical visits), disease-specific exemption registry (which includes identification of subjects exempted from co-paying drugs and services due to their chronic disease condition, including chronic HCV) and related costs (expressed in euros).

2.3 The study population

From the source population we selected the CHC study population according to the following steps (Figure 1).

1. From the source population available in the period 2000-2014 we selected those subjects who met at least one of the following criteria:
    a. had an exemption code for Chronic C Hepatitis (016.070.54),
    b. had an exemption code for Chronic Hepatitis (016.571.4) AND at least one prescription of HCV specific drug (ribavirina, J05AB04). The index date was represented by the first exemption date detected from the above criteria.
2. From the population resulted in point 1 we drop those subjects who:

a. had CLDs other than HCV related (Table 30). To exclude patients who had those CLDs we looked for them among HDs, drug prescriptions or exemption codes occurred before and after the index event (included). This criteria was applied in order to consider those subjects with no other disease than the CHC
b. had exemption for liver transplantation or for being in waiting list for it before the index event (included). The present criteria was applied in order to exlude patients at an advanced stage of the disease for which we cannot go back on time enough to see other elements of the disease
c. were younger than 15 years old at the index event in order to focus on patients out from the pediatric age
d. had incomplete demographic data
e. had exemption in 2000 and in 2014, in order to have at least one year of observatione before and after the index date

The population resulted from the process of selection described in the above 2 steps represented the CHC study population: a cohort of patients which received a new exemption of CHC in 2001-2013.

For each subject of the study population the index date was defined as the date of the first exemption received (step 1). The exemption for chronic HCV had no expiry date in the period under analysis. The index date will be considered as a proxy of the date in which the health care service identifies the subject as being a chronic HCV patient. The index date is the moment from which the observation of the patient starts.

The period of observation before the index date (from a minimum of 1 year to a maximum of 13 years) was used to understand the state of disease at the index date.

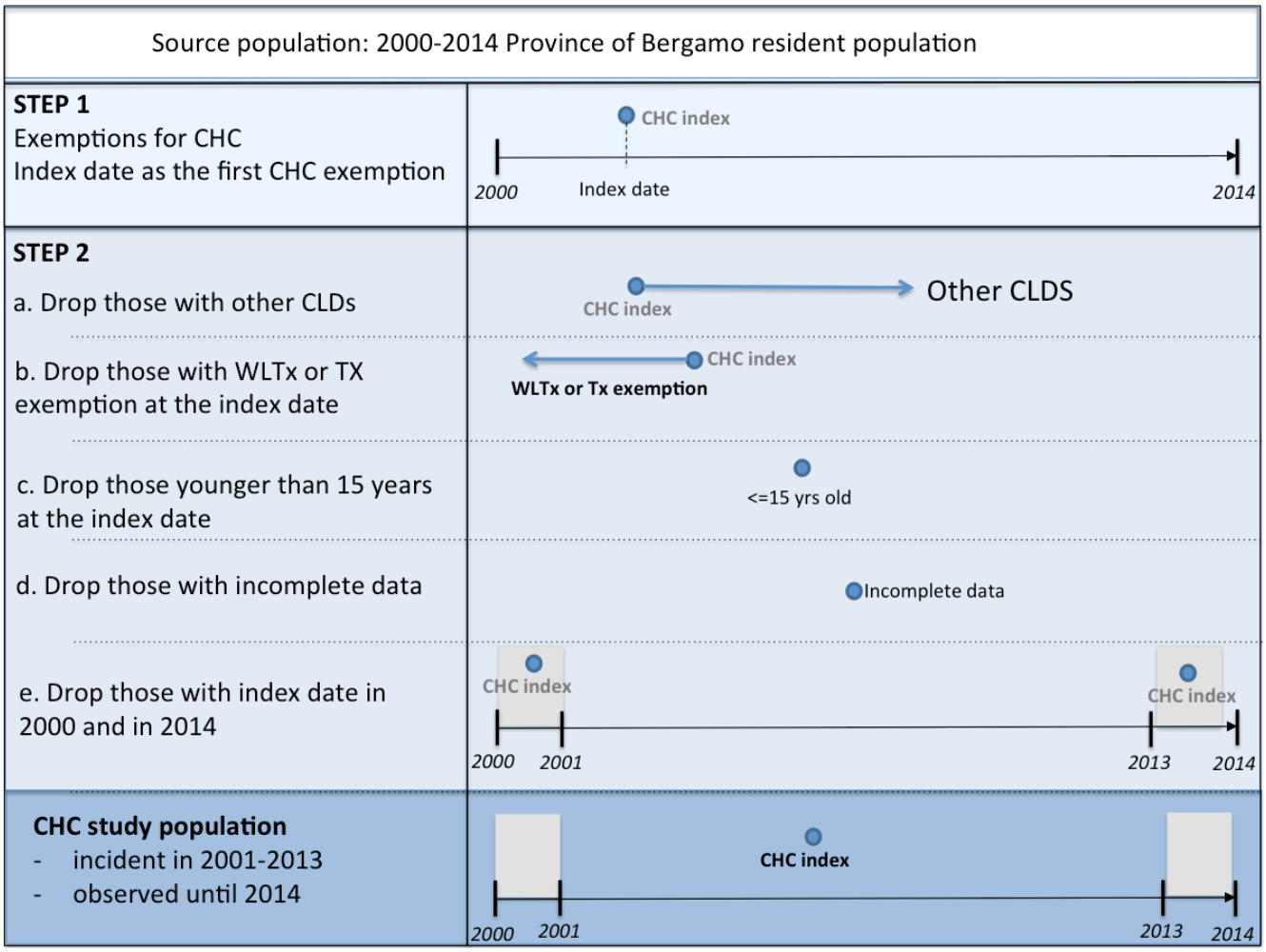
Indeed each patient of the CHC study population was detected at the index date in a specified state of disease:

- CHC state: the patient had a diagnosis of CHC and no other signs of liver progression from the past.

- CIRRHOSIS state, the patient had a diagnosis of CHC and reported evidence of CIRRHOSIS disease progression (detected by exemption and/or HDs concomitant or prior the index date)
- CHC-CIRRHOSIS-DECOMP state, the patient had a diagnosis of CHC and reported evidence of CIRRHOSIS progression (detected by exemption and/or HDs concomitant or prior the index date) and DECOMP.CIRRHOSIS progression (detected by HDs concomitant or prior the index date)
- CHC-HCC state, the patient had a diagnosis of CHC and reported evidence of HCC progression (detected by HDs concomitant or prior the index date)

The study population was followed up from the index date until December 31, 2014 or death or withdrawal from the LHS, whichever came first. We collected all-causes healthcare services use in the study population during the follow-up period. In Figure 1 we reported a schema of the selection process of the CHC study population.

Figure 1. Selection process of the study population



2.4 The not treated study population

The Markov models used in the present work wanted to compare DAAs treatment with no treatment, so we need to keep from the CHC study population those patients who never had prescription of IFN and/or ribavirin. Form the CHC study population we excluded those who had at least a prescription of peginterferon alfa-2b (ATC code L03AB10) and peginterferon alfa-2a (ATC code L03AB11) during the period of observation.

2.5 Methods to describe the source and the CHC study population

The study population was described by sex, age, state of health and comorbidities at the index date.

Age was reported as continuous and categorical variable, in particular we used the following two categorizations: 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75+ and 15-64, 65+.

Baseline characteristics of the study population were summarized as mean or median for quantitative variables, using respectively the standard deviation and the interquartile range in order to give a dispersion measure of them. Categorical variables were reported as absolutes and relative frequencies. Continuous and categorical variables were compared across groups using t-test or non-parametric test and Chi-Square test, respectively. Significant results were those with p-value lower than 5%.

2.6 Comorbidities

Comorbidities of the CHC population were estimated considering the period prior to the index date and was described by using the Deyo-Charlson algorithm [12] that categorizes comorbidities of patients based on HDs diagnoses and associates a weight to each category. The sum of all the weights gives the patient's Charlson Comorbidity Index (CCI): the higher the score the worst is the comorbidity situation for the patient. The Deyo-Charlson algorithm was performed by using the Stagg's Charlson's index Stata 9.2 routine [13].

2.7 Incidence of the CHC

In order to describe the process of detection of the new cases of CHC in the period 2001-2013 we described the study population in terms of incidence on the source population aged over 15 years. In particular the new CHC exemptions within CHC health state at the index date were described as the rate of new CHC exemptions per 100,000 subjects of the source population by age classes and sex per one year. The 95% confidence interval (95% C.I.) of that rate was estimated according to a Poisson distribution. The rate was adjusted by age and sex using the direct standardization method and the 2009 Italian population as standard. The Italian population at 2009 was selected from the Italian National Institute of Statistics [14].

2.8 Standardized Incident Rate

In order to compare the incident of CHC rates between males and females within CHC state accounting for their different age distribution we estimated the age-standardized incident rates. For both males and females we first estimated the incident rates specific for each stratum (age classes), we than multiplied those stratum rates for the weight of the stratum in the standard population (Italy aged over 15 in 2009). Finally we summed up the results in order to obtain the adjusted rate. By multiplying the latter for the population under investigation we estimated its expected number of incident cases if the population had the age structure of the standard one.

2.9 Survival analysis

The overall mortality of the study population was described by the Kaplan-Meier survival analysis. Moreover we applied standardized mortality rates to compare the mortality between the patients in CHC state and the source population accounting for their different distribution by age and sex. Let's call age and sex "stratum". For both population we first estimated the mortality rates specific for each stratum, we than multiplied those stratum rates for the weight of the stratum in the standard population (Italy aged over 15 in 2009). Finally we summed up the results in order to obtain the adjusted rate. Multiplyng the latter for the population under investigation we estimated its expected number of deaths if the population had the age and sex structure of the standard one.

2.10 Progression of disease

We used the standard survival analysis in order to estimate the transition probabilities of the Markov models. From the study population, patient-level time-to-event data were available, where the event was the progression of disease, corresponding to the states reported in the Markov models (Figure 3 and Figure 5). The study population was observed from the index date (the date of the exemption for CHC) until the first progression of disease: this can be detected from HD with diagnosis field related to cirrhosis, decompensated cirrhosis, HCC, LT (see ICD9-CM in **Table 31**) and from anagraphical data for death. From that moment on, the study population will be divided in two groups: one group of those who did not meet any progression of disease during the observational period, so remaining in the CHC state; and onother group of those who change their status from CHC to the one describing the first

progression of disease encountered during the observational period. The latter group of patients will be observed from the moment in which it enters into the new state until the next progression of disease, again detected by HDs or anagraphical data. The process will continue until all states and transition probabilities of the model will be covered by the study population in term of parameters estimation. For each state we had the follow-up time and the number of events during that time. The hazard function of the events was modeled using several parametric model: Weibull, Exponential, Gompertz and log-logistic. Of these we used the one which fitted better the data looking at the likelihood of the regression. The specific parameters of the selected functions and the corresponding cumulative hazard were used to obtain the transition probabilities needed according to the equations:

$$tp = 1 - \frac{S(t)}{S(t-u)} = 1 - \exp[H(t-u) - H(t)]$$

where tp is the transition probability and u represents the cycle length of the model (1 year in our models). So the baseline tp of the event of interest (progression from one state of disease to the next ones) is given by one minus the ratio of the survival function at the end of the interval, S(t), to the survival funcion at the beginning of the interval, S(t-u). The equation can be rewritten in terms of the cumulative hazard, H.

The tranformation of instantaneous hazard rates to discrete time transition probabilities were deeply described by Briggs and colleagues in *Decision Modeling for Health Economic Evaluation* [3].

Observed survival analysis was performed using the Kaplan-Meier non-parametric method and comparisons were tested using the log-rank test.

The progression of disease was performed on the CHC not treated study population since the latter was used to implement the two Markov models.

2.11 Healthcare costs

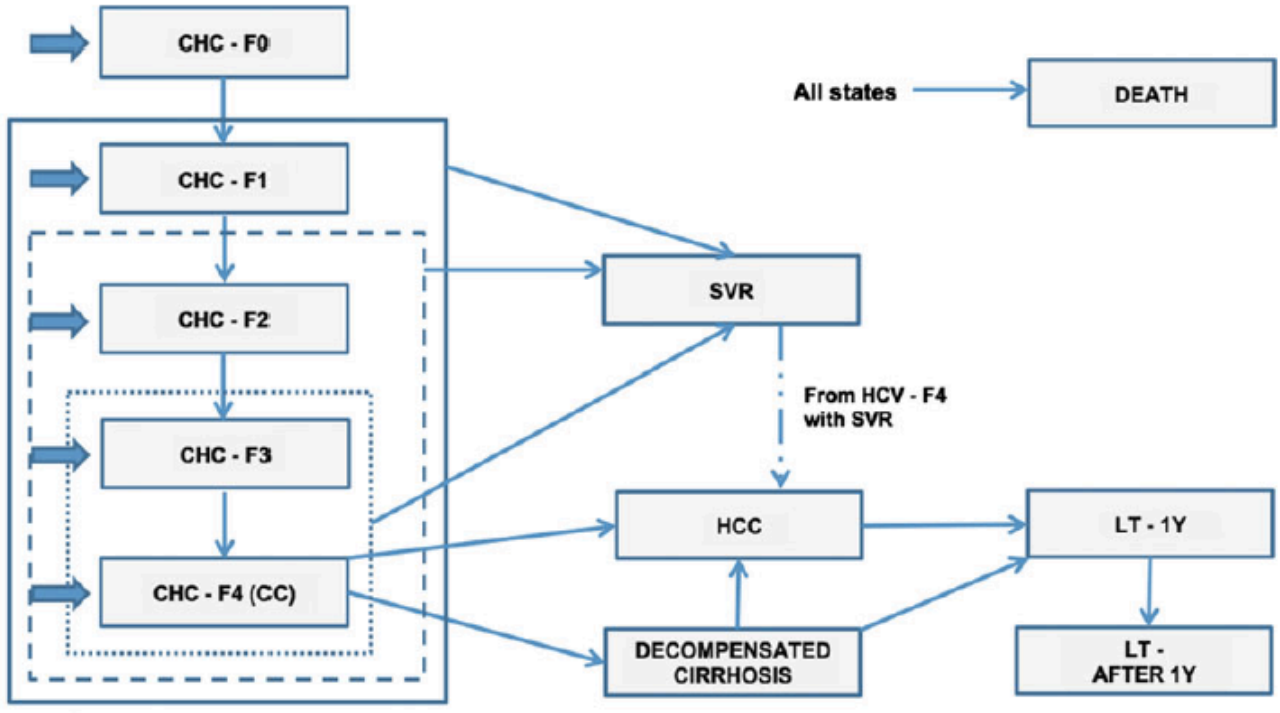
The LHS perspective was the one used to analyze healthcare costs, which were estimated using charges that the LHS reimbursed to the providers of care. The main cost categories

collected into the administrative data were hospitalizations, pharmaceutical prescriptions (drugs) and outpatient claims. Costs were expressed in euros (€). Cost per patient per year was showed and the corresponding confidence interval was calculated using 500 repetitions of bootstrap sampling with replacement [15].

2.12 *The Markov model for young patients*

In Figure 2 we reported the diagrammatic representation of the Markov model built by Cortesi et al [4] to assess the cost-effectiveness of new interferon-free treatment in young CHC patients.

Figure 2. Markov model of Cortesi et al [4].



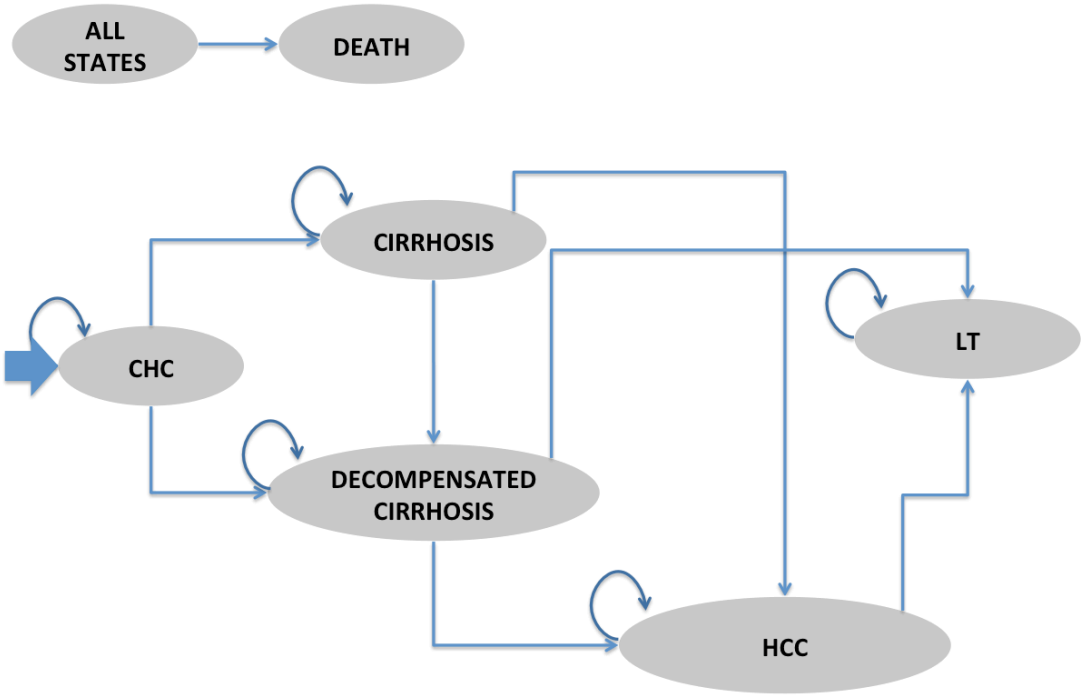
In Figure 3 we reported the diagrammatic representation of the Markov model for young, obtained from the Markov model by Cortesi et al [4] with the following modification:

- CHC-F0, CHC-F1, CHC-F2, CHC-F3 (Chronic Hepatitis C – Fibrosis stage from 0 to 3) states of the first model were collapsed into CHC state of the second ones: this is the

state of CHC patients with no evidence of cirrhosis progression of disease. We collapsed the fribrosis stages because the LHS administrative data don't allow for the definition of the fibrosis stage.

- the CHC-F4 state in the first model (CHC with fibrosis stage equals to 4) correspond to the CIRRHOSIS state in the second ones.
- The SVR state in the first model indicates the Sustained Virologica Response and it was deleted in the second model: the LHS administrative data don't allow for the evaluation of the sustained.
- The LT-1Y and the LT-AFTER 1Y indicate the state of disease Liver Transplanted, which were charactezied by mortality rates in two different period: within one year from LT and after 1 year. The second model did precisely the same even drawing one only ellipse fo LT.

Figure 3. Markov model for young patients



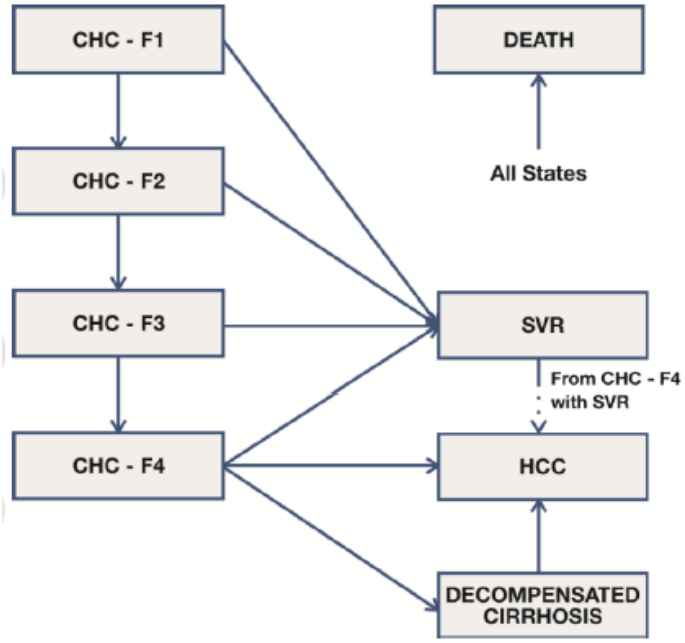
The Markov model for young patients can be read as follows. The entry point is denoted by a large arrow: it indicates that the model starts from considering patients who are in a condition (state) of CHC. According to the progression of the disease, CHC patient could remain in that state or progress to other states represented by ellipses: namely cirrhosis,

decompensated cirrhosis, and death. From the cirrhosis state patients could progress towards decompensated cirrhosis, HCC states, and death. From decompensated cirrhosis patient could progress to HCC, liver transplantation (LT), or death states. From HCC state patient could progress to liver transplantation (LT), or death state.

2.13 The Markov model for elderly

In Figure 4 we reported the diagrammatic representation of the Markov model built by Ciaccio et al [5] to assess the cost-effectiveness of interferon-free treatment on elderly patients (over 65 years old) with CHC, regardless of genotype and previous treatment experience.

Figure 4. Markov model from Ciaccio et al [5]



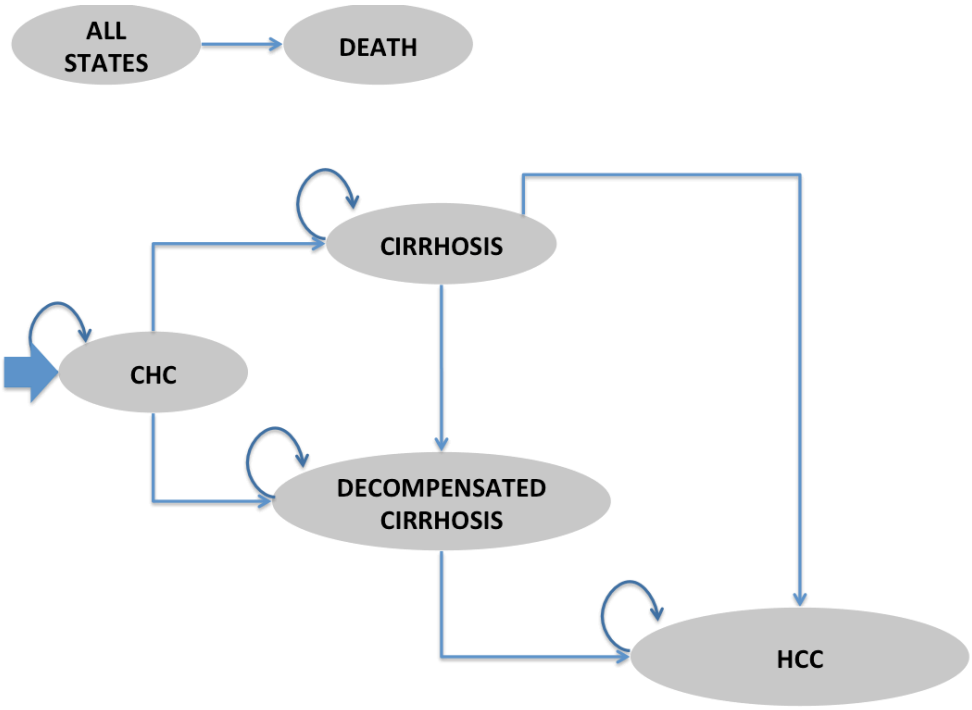
In Figure 5 we reported the diagrammatic representation of the Markov model for elderly, obtained from the Markov model by Ciaccio et al [5] with the following modification:

- CHC-F1, CHC-F2, CHC-F3 (Chronic Hepatitis C – Fibrosis stage from 0 to 3) states of the first model were collapsed into CHC state of the second ones: this is the state of CHC patients with no evidence of cirrhosis progression of disease. We collapsed the

fribrosis stages because the LHS administrative data don't allow for the definition of the fibrosis stage.

- CHC-F4 states in the first model (CHC with fibrosis stage equals to 4) correspond to the CIRRHOSIS state in the second ones.
- The SVR state in the first model indicates the Sustained Virologica Response and it was deleted in the second model: the LHS administrative data don't allow for the evaluation of the sustained.
- The LT state is not considered into the model for elderly because according to the clinical practice transplantation over 65 years old is rare.

Figure 5. Markov model for elderly



The Markov model for elderly can be read as follow. The entry point is denoted by a large arrow: it indicates that the model starts from considering patients who are in a condition (state) of CHC. According to the progression of the disease, CHC patients could remain in that state or progress to cirrhosis or decompensated cirrhosis. Cirrhosis patient could remain in that state or progress to other states represented by ellipses: namely decompensated

cirrhosis, HCC and death. From the decompensated cirrhosis state patients could progress towards HCC state and death. From HCC state patient could progress to death state.

3. Results

3.1 *Source population*

The source population was made by all those individuals resident in the Province of Bergamo during 2000-2013 and aged over 15 years old. The source population was made by around 875 thousand subjects. Its distribution by sex and age was reported in **Figure 6** and **Table 1**.

Figure 6. Source population by age (15-100+) and sex, mean values in 2000-2013

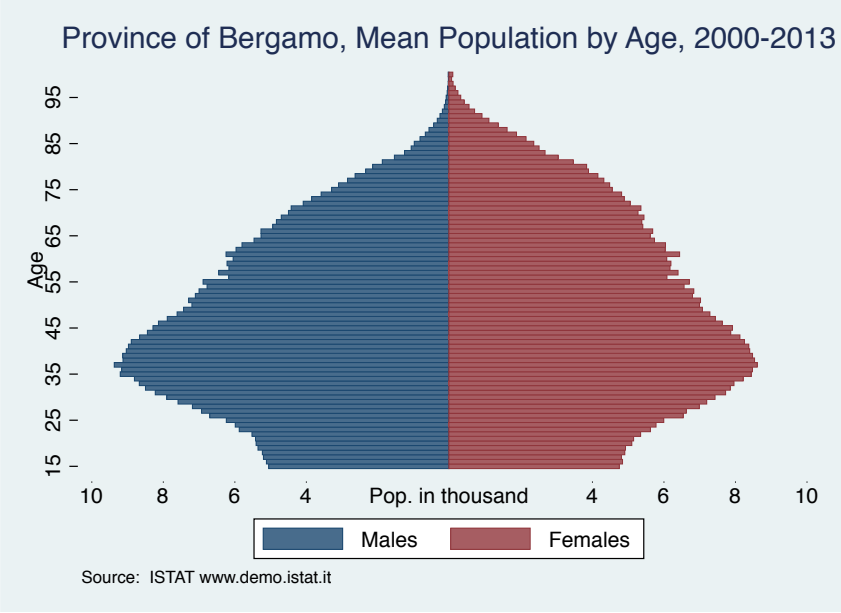


Table 1. Source population (mean number of residents aged 15+ in 2000-2013) by age classes and sex

Age class	FEMALE	% on M&F	MALE	% on M&F	M&F
15-24	51,374	49	54,030	51	105,404
25-34	72,661	49	76,610	51	149,271
35-44	83,689	48	89,881	52	173,571
45-54	71,699	49	74,598	51	146,297
55-64	62,020	50	61,280	50	123,300
subtotal	*341,444*	*49*	*356,399*	*51*	*697,843*
65-74	53,064	54	45,334	46	98,398
75+	51,321	66	26,575	34	77,896
subtotal	*104,385*	*59*	*71,909*	*41*	*176,294*
Total	**445,829**	**51**	**428,308**	**49**	**874,137**

3.2 *The CHC study population*

The application of the selection algorithm (Figure 1) to the source population resulted in the study population described in Figure 7 and Table2.

Figure 7. Process of selection of the CHC study population

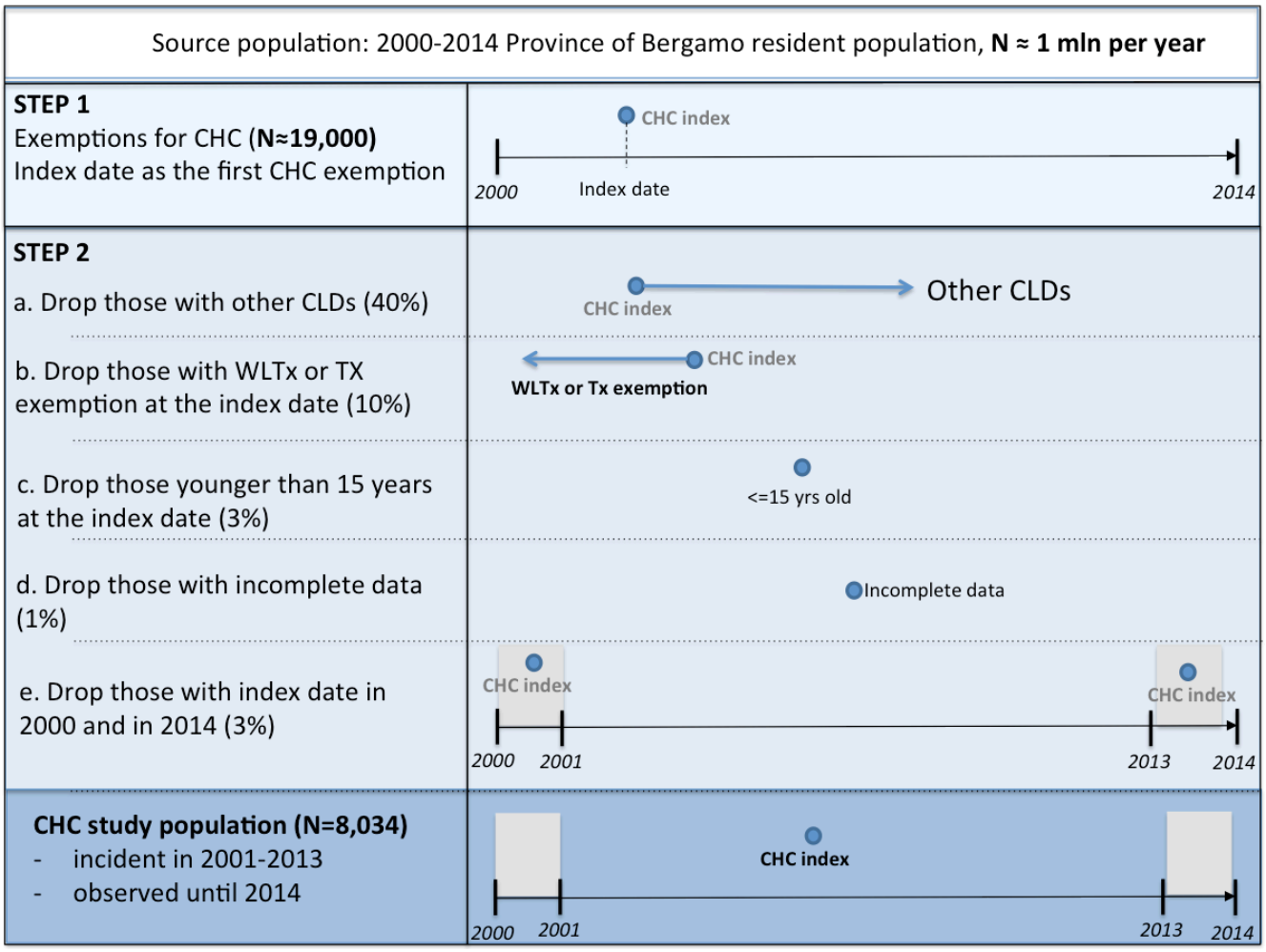
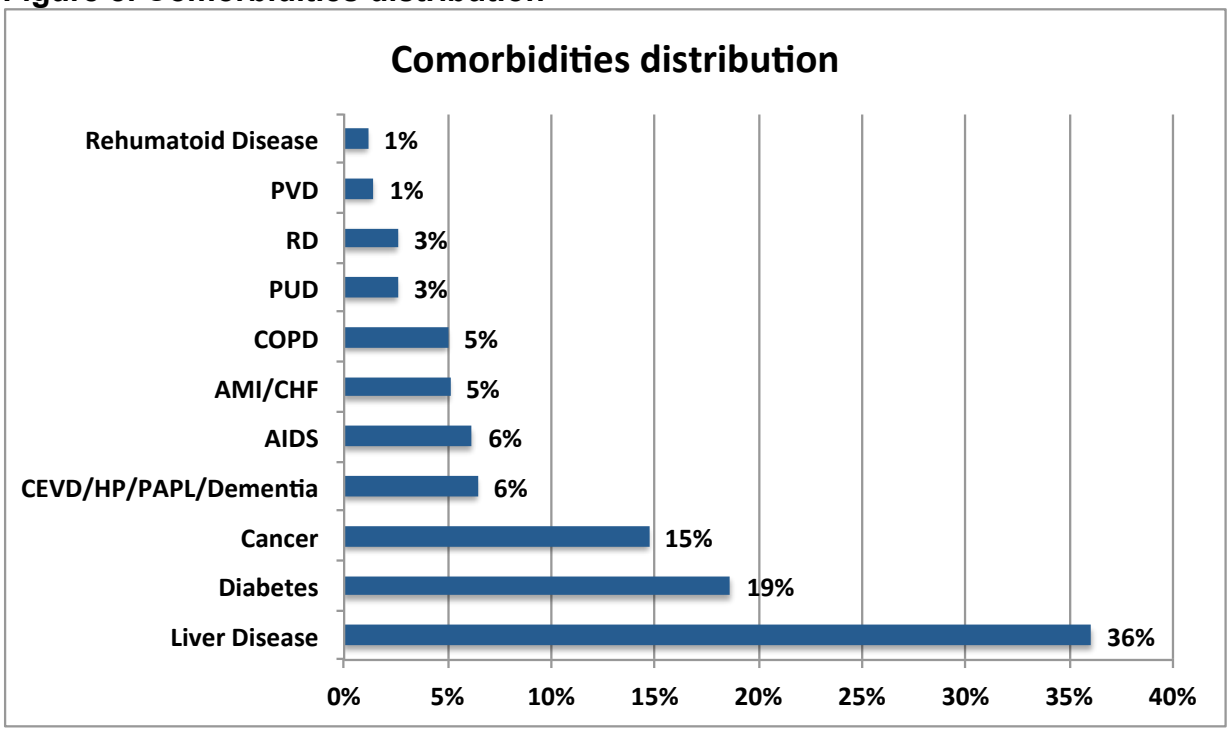


Table 2. The CHC study population by age, sex and state of disease at the index date

Variables	State of disease at index date				
	CHC	CIRRHOSIS	DECOMP. CIRRHOSIS	HCC	Total
N (% on Total)	7,785 (96.9)	195 (2.4)	30 (0.4)	24 (0.3)	8,034 (100)
Male %	55	61	60	75	56
Mean age (SD), years	48.5 (13.7)	57.9 (11.5)	58.1 (13.0)	65.6 (7.2)	48.8 (13.8)
Median age (min-max), years	48 (15-91)	61 (30-85)	58 (36-90)	66 (53-77)	49 (15-91)
Age classes, N (%)					
15-24	213 (3)	0 (0)	0 (0)	0 (0)	213 (3)
25-34	1166 (15)	5 (3)	0 (0)	0 (0)	1,171 (17)
35-44	1944 (25)	28 (14)	4 (13)	0 (0)	1,976 (42)
45-54	1523 (20)	36 (18)	9 (30)	3 (13)	1,571 (61)
55-64	1974 (25)	61 (31)	8 (27)	6 (25)	2,049 (87)
subtotal	*6,820 (87)*	*130 (67)*	*21 (70)*	*9 (37)*	*6,980 (87)*
65-74	827 (11)	53 (27)	7 (23)	12 (50)	899 (98)
75+	138 (2)	12 (6)	2 (7)	3 (13)	155 (100)
subtotal	*965 (13)*	*65 (33)*	*9 (30)*	*15 (63)*	*1,054 (13)*
Years of observation					
median	10.1	3.8	1.6	1.8	--
p5	2.1	0.1	0.1	0.1	--
p95	13.8	13.3	9.3	8.4	--
Mean CCI (SE)	0.2 (0.09)	1.2 (0.12)	3.07 (0.39)	3.17 (0.18)	0.23 (0.01)

The study population was made of 8,034 subjects. At the index date 97% of the study population was in CHC state of disease, 2% was in CIRRHOSIS state and the remaining 1% was in other states of disease reported in Table 2. The mean value of the CCI increases with the worsening of the disease condition. An overall description of the main comorbidities of the study population detected at the index date is shown in Figure 8. At the end of 2014, 9 subjects on 1,000 aged over than 15 years was a subject with a chronic hepatic condition.

Figure 8. Comorbidities distribution



PVD, peripheral vascular disease; RD, renal disease; PUD, peptic ulcer disease; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; CHF, chronic heart failure; CEVD, cerebrovascular disease;HP, hemiplegia; PAPL, paraplegia.

The percentages showed in the above figure are calculated on those who reported comorbidities by HDs previous index date (N=1,115). Comorbidities can be concomitant.

3.3 *Standardized Incidence Rates for CHC patients*

In Figure 9 we reported the rate of new CHC cases (only those detected in CHC state) by age classes and sex express as 100,000 subjects of the source population per one year.

Figure 9. The average, annual incidence rate of CHC occurrence (x100,000 subjects) by age classes and sex (N=7,785)

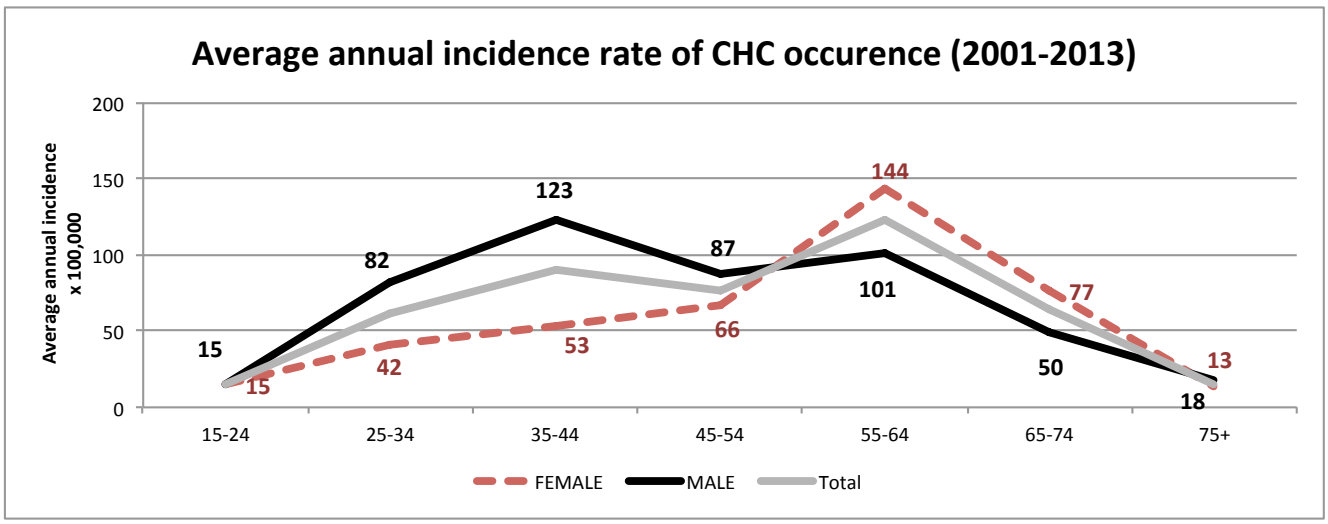


Table 3. 95% C.I. of rate of chronic CHC occurrence (x100,000 subjects per year), by age classes and sex

Age class	FEMALE	MALE	Total
15-24	12.4-18.3	12.4-18.2	13.2-17.3
25-34	37.5-45.9	75.9-87.5	58.4-65.6
35-44	49.0-57.9	117.0-130.1	85.6-93.6
45-54	61.3-71.7	81.4-93.0	73.1-80.9
55-64	135.7-152.3	94.0-108.0	117.2-128.1
65-74	70.5-83.7	44.4-55.9	60.1-69.0
75+	10.6-16.6	13.3-22.9	12.4-17.5

The average, annual, crude, all-ages rate of new diagnosis of CHC was 69 (62-73)x100,000: 78 (70-87) and 60 (53-68) for male and female, respectively. If the two population of males and females had the age distribution of the standard population (the Italian ones in 2009), the corresponding age-adjusted incidence rates would have been 76 and 60.

Table 4. Annual, average, age-adjusted incidence rates of new CHC cases for males

Age Class	Average Pop	Annual Average Cases	Pop Dist	Stratum Rates (s)	Stnd Pop Dist (P)	s*P
15-64	354,590	305	0.835	0.0009	0.76	0.0007
65+	69,901	27	0.165	0.0004	0.24	0.0001
Total	424,491	332				
Crude rate (x 100,000) (95% C.I.)			**78 (70-87)**			
Age-Adj Rate (x 100,000) (95% C.I.)			**76 (70-80)**			
Expected Cases (N)			**316**			

Table 5. Annual, average, age-adjusted incidence rates of new CHC cases for females

Age Class	Average Pop	Annual Average Cases	Pop Dist	Stratum Rates (s)	Stnd Pop Dist (P)	s*P
15-64	341,950	220	0.773	0.0006	0.76	0.0005
65+	100,568	47	0.227	0.0005	0.24	0.0001
Total	442,518	267				
Crude rate (x 100,000) (95% C.I.)			**60.4 (53-68)**			
Age-Adj Rate (x 100,000) (95% C.I.)			**60 (50-70)**			
Expected Cases (N)			**266**			

3.4 *Standardized Mortality Rates for CHC patients*

The estimation of the mortality rates of the source (province of Bergamo) and the study population in CHC state of disease (Table 6 and **Table 7**) showed that the latter had a mortality not higher than the former population. This result will be involved in the population of the Markov model for young patients in relation of the mortality rate of patients in CHC state.

Table 6. Annual, average, age-adjusted mortality rates of the source population

Age Class and sex	Average Pop	Annual Average Cases	Pop Dist	Stratum Rates (s)	Stnd Pop Dist (P)	s*P
15-64, f	349,859	910	0.396	0.0014	0.37	0.0005
15-64, m	350,397	487	0.397	0.0026	0.38	0.001
65+, f	90,483	6,495	0.102	0.0763	0.15	0.0114
65+, m	92,499	6,900	0.105	0.0702	0.1	0.007
Total	883,238	14,793				
Crude rate x 100 (95% C.I.)		**1.67 (1.65-1.70)**				
Age-Sex Adj Rate x 100 (95% C.I.)		**1.99 (1.96-2.03)**				
Expected Cases (N)		**17,576**				

Table 7. Annual, average, age-adjusted mortality rates of the CHC study population

Age Class and sex	Average Pop	Annual Average Cases	Pop Dist	Stratum Rates (s)	Stnd Pop Dist (P)	s*P
15-64, f	2861	3	0.37	0.001	0.37	0.00041
15-64, m	3959	6	0.51	0.002	0.38	0.00062
65+, f	614	2	0.08	0.003	0.15	0.00051
65+, m	351	2	0.05	0.004	0.1	0.00044
Total	7,785	13				0.00197
Crude rate x 100 (95% C.I.)		**0.17 (0.09-0.29)**				
Age-Sex Adj Rate x 100 (95% C.I.)		**0.20 (0.08-0.32)**				
Expected Cases (N)		**15**				

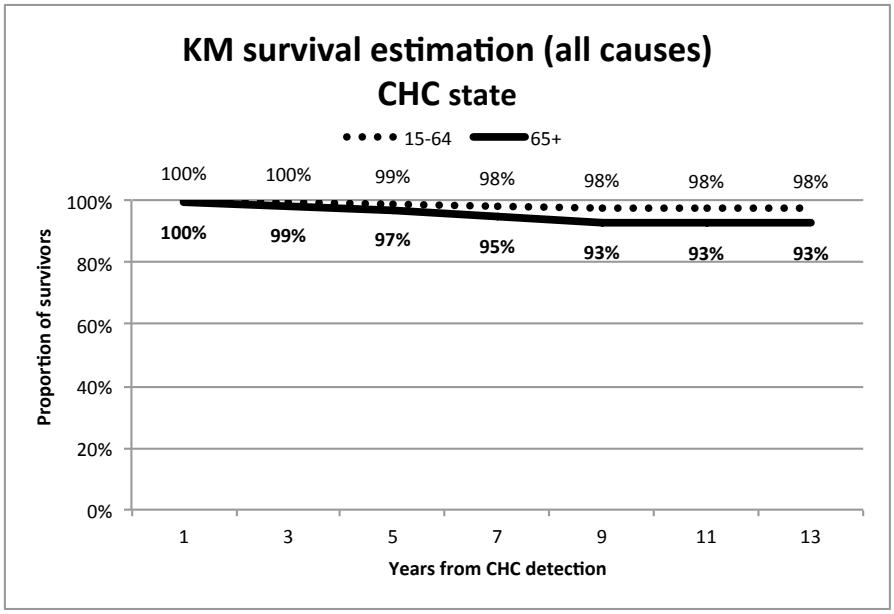
3.5 *Survival analysis for the CHC study population by state of disease*

The all-ages mortality rate of those patients of the study population detected in CHC state was equal to 2.3 deaths per 1,000 patient-year, 1,9 and 6.3 for young and older patients, respectively (**Table 8**). Looking at the Kaplan-Meier longitudinal graph we see that 99% and 97% of patients were alive after 5 years from the index date (detection of CHC) in young and elderly patients, respectively. The survival propotions decreased to 98% and 93% in the last year of observation (**Figure 10**). The difference between age groups was statistically significant.

Table 8. Mortality rates (x1,000 pt-years) in CHC state of disease

Age	N	%	person-years	failures	rate (x1,000)	95% ll	95% ul	Median time of obs (yrs)
15-64	6,820	88%	66,584	125	1.9	1.6	2.2	10.5
65+	965	12%	7,452	47	6.3	4.7	8.4	7.0
total	**7,785**	**100%**	**74,036**	**172**	**2.3**	**2.0**	**2.7**	**10.1**

Figure 10. Kaplan-Meier survival estimation in CHC state of disease



Log-rank test for equality of survival functions:

chi2(1)=51.98

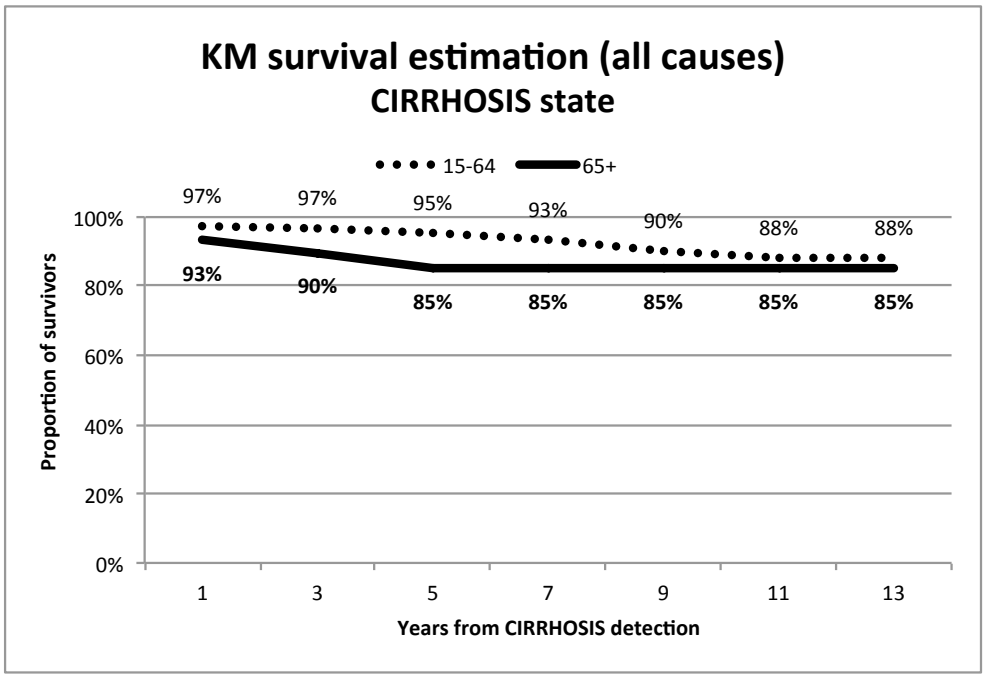
p>chi2<1%

The all-ages mortality rate of those patients of the study population detected in CIRRHOSIS state was equal to 14.9 deaths per 1,000 patient-year, 10.5 and 24.7 for young and older patients, respectively (**Table 9**). Looking at the Kaplan-Meier longitudinal graph we see that 95% and 85% of patients were alive after 5 years from the index date (detection of CIRRHOSIS) in young and elderly patients, respectively. The survival propotions decreased to 88% and 85% in the last year of observation (**Figure 11**). The difference between age groups was statistically significant.

Table 9. Mortality rates (x1,000 pt-years) in CIRRHOSIS state of disease

Age	N	%	person-years	failures	rate (x1,000)	95% ll	95% ul	Median time of obs (yrs)
15-64	270	62%	1,904	20	10.5	6.8	16.3	4.9
65+	166	38%	849	21	24.7	16.1	37.9	2.6
total	**436**	**100%**	**2,753**	**41**	**14.9**	**11.0**	**20.2**	**3.8**

Figure 11. Kaplan-Meier survival estimation in CIRRHOSIS state of disease



Log-rank test for equality of survival functions:

chi2(1) = 5.63

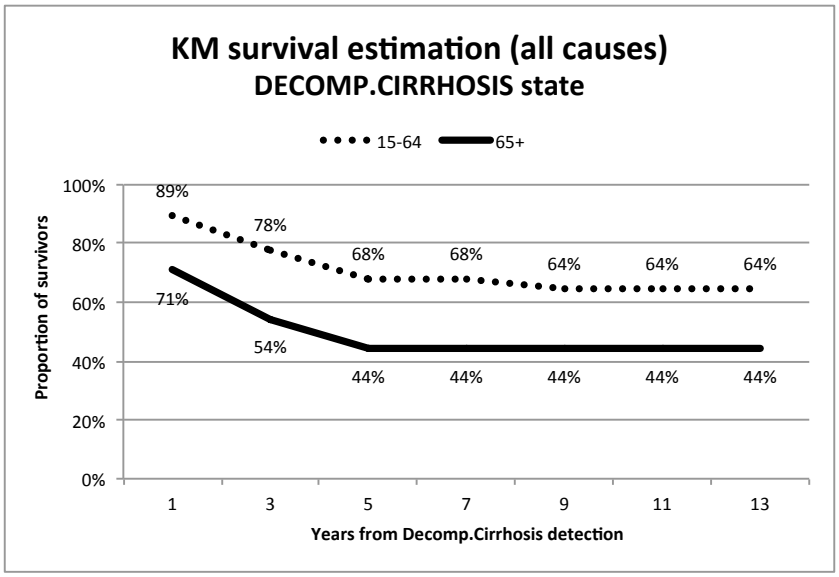
p>chi2 < 5%

The all-ages mortality rate of those patients of the study population detected in DECOMPENSATED CIRRHOSIS state was equal to 101.5 deaths per 1,000 patient-year, 62.0 and 205.8 for young and older patients, respectively (**Table 10**). Looking at the Kaplan-Meier longitudinal graph we see that 68% and 44% of patients were alive after 5 years from the index date (detection of DECOMPENSATED CIRRHOSIS) in young and elderly patients, respectively. The survival propotions decreased to 64% and 44% in the last year of observation (**Figure 12**). The difference between age groups was statistically significant.

Table 10. Mortality rates (x1,000 pt-years) in DECOMPENSATED CIRRHOSIS state of disease

Age	N	%	person-years	failures	rate (x1,000)	95% ll	95% ul	Median time of obs (yrs)
15-64	125	55%	500	31	62.0	43.6	88.2	1.9
65+	104	45%	189	39	205.8	150.4	281.7	1.1
total	**229**	100%	**689**	**70**	**101.5**	**80.3**	**128.3**	**1.6**

Figure 12. Kaplan-Meier survival estimation in DECOMPENSATED CIRRHOSIS state of disease



Log-rank test for equality of survival functions:

chi2(1) = 12.50

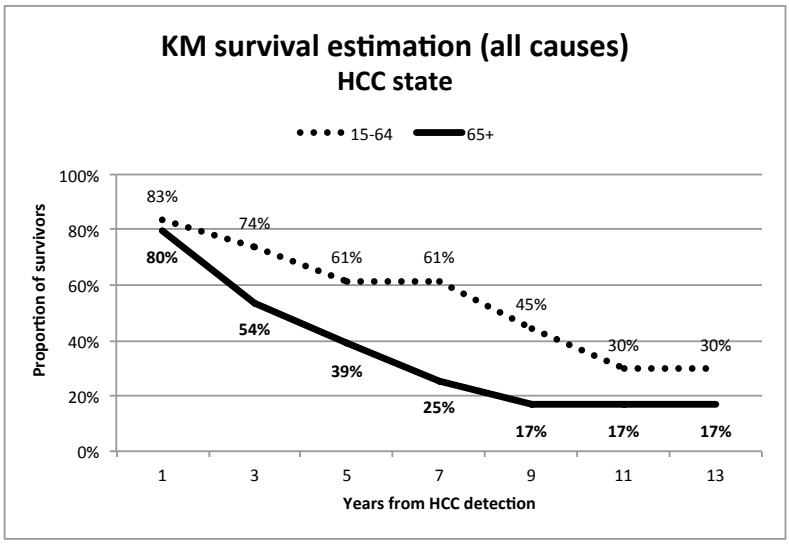
p>chi2 < 1%

The all-ages mortality rate of those patients of the study population detected in HCC state was equal to 147.1 deaths per 1,000 patient-year, 104.5 and 192.0 for young and older patients, respectively (**Table 11**). Looking at the Kaplan-Meier longitudinal graph we see that 61% and 39% of patients were alive after 5 years from the index date (detection of HCC) in young and elderly patients, respectively. The survival propotions decreased to 30% and 17% in the last year of observation (**Figure 13**). The difference between age groups was statistically significant.

Table 11. Mortality rates (x1,000 pt-years) in HCC state of disease

Age	N	%	person-years	failures	rate (x1,000)	95% ll	95% ul	Median time of obs (yrs)
15-64	57	220	23	104.5	69.5	157.3	241.3	1.4
65+	69	208	40	192.0	140.8	261.7	825.1	2.1
total	**126**	**428**	**63**	**147.1**	**114.9**	**188.3**	**329.9**	**1.8**

Figure 13. Kaplan-Meier survival estimation in HCC state of disease



Log-rank test for equality of survival functions:

chi2(1) = 5.10

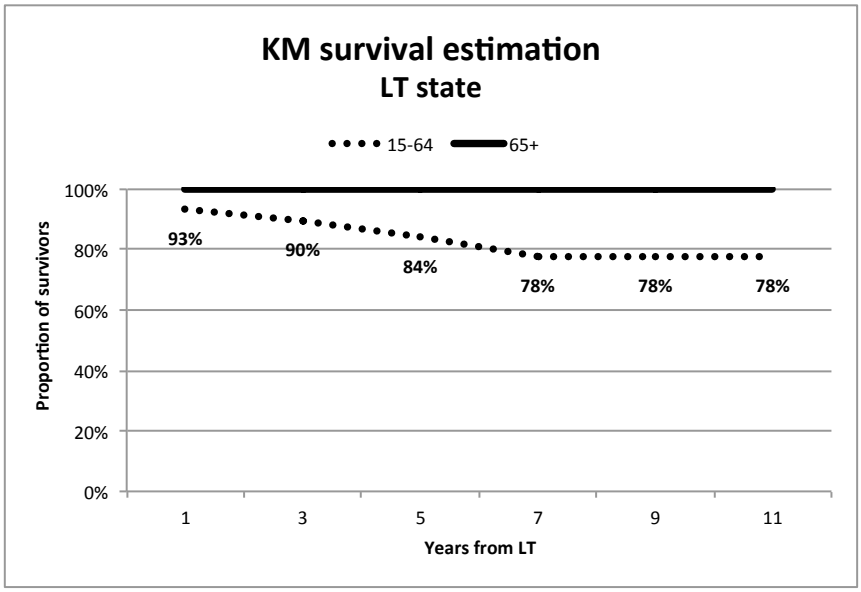
p>chi2 < 5%

The all-ages mortality rate of those patients of the study population detected in LT state was equal to 29.4 deaths per 1,000 patient-year. According to the clinical practice, LT is rarely performed on elderly patients. As showed in **Table 12** the available data found only 2 patients aged over 65 years and who received a liver transplantation. For them the data did not registered deaths: we had to stress that they were observed for a very short time, 8 year in total. Looking at the Kaplan-Meier longitudinal graph we see that 84% of young patients were alive after 5 years from the index date (detection of LT). The survival propotion decreased to 73% in the last year of observation (**Figure 13**).

Table 12. Mortality rates (x1,000 pt-years) in LT state of disease

Age	N	%	person-years	failures	rate (x1,000)	95% ll	95% ul	Median time of obs (yrs)
15-64	32	94%	161	5	31.0	12.9	74.4	4.2
65+	2	6%	8	0	0.0	.	.	4.3
total	**34**	**100%**	**170**	**5**	**29.4**	**12.2**	**70.7**	**4.2**

Figure 14. Kaplan-Meier survival estimation in LT state of disease



Log-rank test for equality of survival functions:

chi2(1) = 0.21

p>chi2 = 0.64

3.6 *Not treated study population*

The Markov models used in the present work wanted to compare DAAs treatment with no treatment, so we need to keep from the study population those patients who never had prescription of PEG-IFNα and ribavirin, representing the 53% of the study population. The not treated study population is described in **Table 13**.

Table 13. The not treated study population by age, sex and state of disease at the index date

Variables	State of disease at index date				Total
	CHC	CIRRHOSIS	DECOMP. CIRRHOSIS	HCC	
N (% on Total)	4,086 (96.6)	102 (2.4)	23 (0.5)	20 (0.5)	4,231 (100)
Male %	50	53	52	70	50
Mean age (SD), years	50.3 (14.5)	61.2 (10.4)	59.5 (14.1)	66.7 (6.7)	50.7 (14.6)
Median age (min-max), years	52 (15-91)	63 (37-85)	59 (36-90)	67.5 (54-77)	49 (15-91)
Age classes, N (%)					
15-24	110 (3)	0 (0)	0 (0)	0 (0)	110 (3)
25-34	600 (15)	0 (0)	0 (0)	0 (0)	600 (14)
35-44	859 (21)	9 (9)	4 (17)	0 (0)	872 (21)
45-54	690 (17)	16 (16)	4 (17)	1 (5)	711 (17)
55-64	1,112 (27)	35 (34)	7 (30)	5 (25)	1,159 (27)
subtotal	*3,371 (83)*	*60 (59)*	*15 (65)*	*6 (30)*	*3,452 (81)*
65-74	*588 (14)*	33 (32)	*6 (26)*	11 (55)	638 (15)
75+	127 (3)	9 (9)	2 (9)	3 (15)	141 (3)
subtotal	*715 (17)*	*42 (41)*	*8 (35)*	*17 (70)*	*779 (18)*
Years of observation					
median	10.3	2.9	1.5	1.6	--
p5	1.7	0.1	0.1	0.1	--
p95	13.9	12.8	8.0	9.1	--
Mean CCI (SE)	0.2 (0.01)	1.2 (0.15)	2.7 (0.40)	3.2 (0.21)	0.23 (0.01)

Table 14. Annual, average, age-adjusted mortality rates of the not treated study population

Age Class and sex	Average Pop	Annual Average Cases	Pop Dist	Stratum Rates (s)	Stnd Pop Dist (P)	s*P
15-64, f	1576	2	0.386	0.0013	0.37	0.0005
15-64, m	1795	4	0.439	0.0022	0.38	0.0008
65+, f	462	2	0.113	0.0043	0.15	0.0006
65+, m	253	1	0.062	0.004	0.1	0.0004
Total	4,086	9				
Crude rate x 100 (95% C.I.)		**0.22 (0.10-0.41)**				
Age-Sex Adj Rate x 100 (95% C.I.)		**0.23 (0.08-0.39)**				
Expected Cases (N)		**9.4**				

The estimation of the mortality rates of the source and the not treated study population in CHC state of disease (Table 6 and **Table 14**) showed that the latter had a mortality not higher than the former population. This result will be involved in the population of the Markov model for young patients in relation of the mortality rate of patients in CHC state.

3.7 *Progression of disease rates of the not treated population*

Table 15. Progression rates per 1,000 person-years from CHC status

from CHC to CIRRHOSIS							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	32625	87	2.7	2.2	3.3	39.85	<1%
65+	5229	45	8.6	6.4	11.5		
total	**37854**	**132**	**3.5**	**2.9**	**4.1**		
from CHC to DECOMP. CIRRHOSIS							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	32625	46	1.4	1.1	1.9	22.14	<1%
65+	5229	23	4.4	2.9	6.6		
total	**37854**	**69**	**1.8**	**1.4**	**2.3**		
from CHC to DEATH (all causes)							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	32625	84	2.6	2.1	3.2	59.8	<1%
65+	5229	40	7.6	5.6	10.4		
total	**37854**	**124**	**3.3**	**2.7**	**3.9**		

Table 16. Progression of disease per 1,000 person-years from CIRRHOSIS status

from CIRRHOSIS to DECOMP.CIRRHOSIS							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	587	26	44.3	30.1	65.0	1.99	0.1579
65+	399	29	72.6	50.4	104.5		
total	**987**	**55**	**55.7**	**42.8**	**72.6**		
from CIRRHOSIS to HCC							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	587	25	42.6	28.8	63.0	0.43	0.51
65+	399	23	57.6	38.3	86.6		
total	**987**	**48**	**48.6**	**36.7**	**64.5**		
from CIRRHOSIS to DEATH (all causes)							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	587	14	23.8	14.1	40.2	3.0	0.086
65+	399	20	50.1	32.3	77.6		

total	**987**	**34**	**34.5**	**24.6**	**48.2**

Table 17. Progression of disease per 1,000 person-years from DECOMP. CIRRHOSIS status

from DECOMP. CIRRHOSIS to HCC							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	221	9	40.7	21.2	78.2	0.1	0.76
65+	132	6	45.6	20.5	101.4		
total	**353**	**15**	**42.5**	**25.6**	**70.5**		
from DECOMP. CIRRHOSIS to Tx							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	221	6	27.1	12.2	60.4	5.1	0.023
65+	132	0	0.0	.	.		
total	**353**	**6**	**17.0**	**7.6**	**37.8**		
from DECOMP. CIRRHOSIS to Dx (all causes)							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	221	23	104.0	69.1	156.5	5.3	0.021
65+	132	32	242.9	171.8	343.5		
total	**353**	**55**	**155.8**	**119.6**	**203.0**		

Table 18. Progression of disease per 1,000 person-years from HCC status

from HCC union to Tx							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	86	5	58.3	24.3	140.0	8.1	<1%
65+	138	0	0.0	.	.		
total	**224**	**5**	**22.4**	**9.3**	**53.7**		
from HCC union to Dx (all causes)							
age classes	**person-years**	**failures**	**rate (x1,000)**	**95% LL**	**95% UL**	**chi2**	**p**
15-64	86	18	209.8	132.2	333.0	0.2	0.7
65+	138	30	217.6	152.1	311.2		
total	**224**	**48**	**214.6**	**161.7**	**284.8**		

Table 19. Progression of disease per 1,000 person-years from LT status

	from Tx union to Dx (liver related)						
age classes	person-years	failures	rate (x1,000)	95% LL	95% UL	chi2	p
15-64	161	0	.	.	.	.	.
65+	8	0	.	.	.	.	
total	170	0	.	.	.	.	

Table 20. Transition probabilities for patients 15-64 years old

State of disease	CHC	CIRRHOSIS	DEC.CIRR.	HCC	LT	DEATH (all causes)
CHC	99.3%	0.3%	0.1%	--	--	0.3%
CIRRHOSIS		89.1%	4.3%	4.2%	--	2.4%
DEC.CIRR.			83.5%	4.0%	2.7%	9.9%
HCC				71.6%	5.7%	22.8%
LT					--	--
DEATH						100.0%

Table 21. Transition probabilities for patients 65+ years old

State of disease	CHC	CIRRHOSIS	DEC.CIRR.	HCC	LT	DEATH (all causes)
CHC	97.9%	0.9%	0.4%	--	--	0.8%
CIRRHOSIS		82.5%	7.0%	5.6%	--	4.9%
DEC.CIRR.			74.0%	4.5%	--	21.6%
HCC				80.4%	--	19.6%
LT					--	--
DEATH						100.0%

Table 22. Mean cost per patient per year by phase of disease (study population)

Phase of disease	N	Mean cost per year	Boot SE	95% ll	95% up
CHC state					
15-64	965	2,786	114.0	2,563	3,010
65+	6,820	2,170	44.0	2,084	2,256
Total	7,785	2,230	39.9	2,151	2,308
Cirrhosis state					
15-64	270	3,840	255.4	3,340	4,341
65+	166	4,095	328.2	3,452	4,738
Total	436	3,917	201.2	3,523	4,311
Decompensated cirrhosis state					
15-64	125	8,157	1,408.3	5,397	10,917
65+	104	8,808	875.5	7,092	10,524
Total	229	8,359	1,022.6	6,355	10,364
HCC state					
15-64	57	10,381	770.6	8,871	11,892
65+	69	8,891	975.4	6,979	10,802
Total	126	9,504	655.9	8,219	10,790
Liver transplantation (within 1 yr)					
15-64	32	93,358	3,566.9	86,367	100,349
65+	2	112,487	13,836.5	85,367	139,606
Total	34	93,358	3,566.9	86,367	100,349
Liver transplantation (after 1 yr)					
15-64	32	7,783	1115.5	7.0	0.000
65+	2	15,161	7407.9	2.1	0.041
Total	34	8,162	1135.7	7.2	0.000

Figure 15. Mean cost per patient per year by phase of disease (study population)

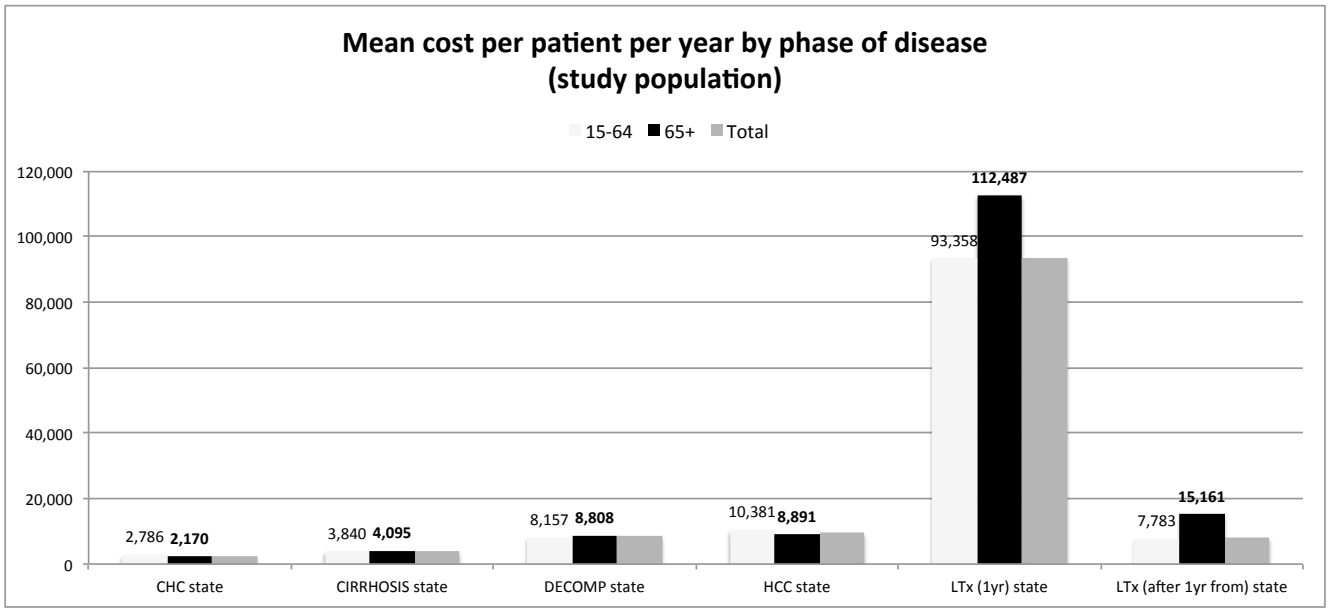


Table 23. Mean cost per patient per year by phase of disease (not treated study population)

Phase of disease	N	Mean cost per year	Boot SE	95% ll	95% up
CHC state					
15-64	3,371	1,335	37.3	1,262	1,409
65+	715	2,457	129.1	2,204	2,710
Total	4,086	1,490	36.2	1,419	1,561
Cirrhosis state					
15-64	119	3,464	425.8	2,630	4,299
65+	115	3,967	321.0	3,338	4,597
Total	234	3,668	288.0	3,103	4,232
Decompensated cirrhosis state					
15-64	68	8,495	2447.6	3,698	13,293
65+	79	8,609	933.8	6,778	10,439
Total	147	8,538	1440.3	5,715	11,361
HCC state					
15-64	29	9,578	984.3	7,649	11,507
65+	47	9,204	1359.3	6,539	11,868
Total	76	9,347	904.5	7,575	11,120
Liver transplantation (within 1 yr)					
15-64	10	97,635	6319.6	85,249	110,021
65+	1	92,967	--	--	--
Total	11	97,211	5367.4	86,691	107,731
Liver transplantation (after 1 yr)					
15-64	10	5,989	684.6	4,647	7,331
65+	1	22,974	--	--	--
Total	11	5,846	598.8	4,672	7,019

Figure 16. Mean cost per patient per year by phase of disease (not treated study population)

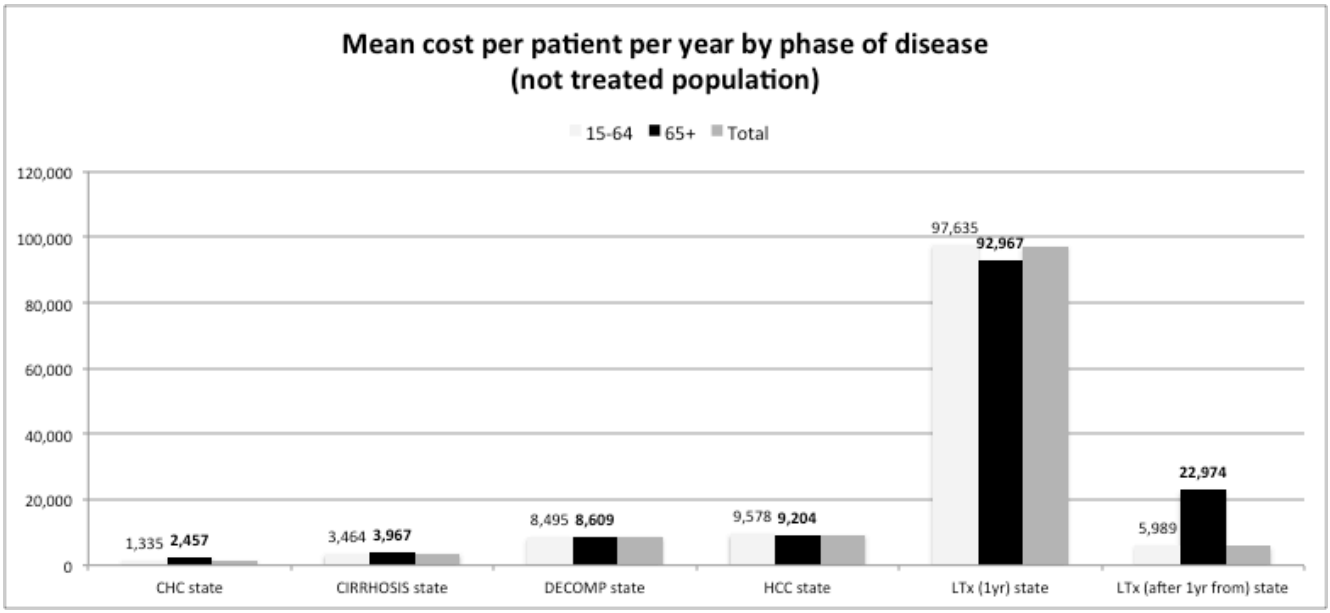


Table 24. Markov model for young patients treated in CHC status: Cortesi et al [4] versus LHS results

Cortesi et al. [4]			Results per patient (deterministic): time horizon lifetime				
Treated in CHC state				Cost	QALYs	LYs	
(Mean age=51)			CHC treated	€21,420	18.8	34.8	
			Not treated	€14,718	16.1	27.9	
			Trt vs NoTrt (ICER)	€2,479	per QALY	€971	per LY
			Δ	€6,702	2.7	6.9	
LHS - Probability Transitions			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	**LHS**					
CHC --> CIRRHOSIS	0.014	0.0027		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,052	18.9	35.0	
			Not treated	€11,044	17.1	30.1	
			Trt vs NoTrt (ICER)	**€5,411**	**per QALY**	€2,012	per LY
			Δ	€10,009	1.8	5.0	
CIRRHOSIS --> DC	0.042	0.043		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,053	18.9	35.0	
			Not treated	€11,048	17.1	30.1	
			Trt vs NoTrt (ICER)	**€5,406**	**per QALY**	€2,010	per LY
			Δ	€10,005	1.9	5.0	
CIRRHOSIS --> HCC	0.033	0.042		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,057	18.9	35.0	
			Not treated	€11,087	17.1	30.0	
			Trt vs NoTrt (ICER)	**€5,354**	**per QALY**	€1,992	per LY
			Δ	€9,969	1.9	5.0	
DC--> HCC	0.058	0.040		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,057	18.9	35.0	
			Not treated	€11,088	17.1	30.0	
			Trt vs NoTrt (ICER)	**€5,359**	**per QALY**	€1,994	per LY
			Δ	€9,968	1.9	5.0	
DC --> LT	0.009	0.027		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,065	18.9	35.0	
			Not treated	€11,170	17.1	30.0	
			Trt vs NoTrt (ICER)	**€5,325**	**per QALY**	€1,981	per LY
			Δ	€9,895	1.9	5.0	
HCC --> LT	0.108	0.057		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,054	18.9	35.0	
			Not treated	€11,062	17.1	30.0	
			Trt vs NoTrt (ICER)	**€5,367**	**per QALY**	€1,997	per LY
			Δ	€9,992	1.9	**5.0**	
LHS - Probability of Death			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	**LHS**					
CHC	1.79	1.00		**Cost**	**QALYs**	**LYs**	
			CHC treated	€21,153	19.1	35.5	

			Not treated	€12,053	18.7	34.7	
			Trt vs NoTrt (ICER)	**€20,496**	**per QALY**	€10,561	per LY
			Δ	**€9,100**	**0.4**	**0.9**	
				Cost	**QALYs**	**LYs**	
CIRRHOSIS	0.032	0.024	**CHC treated**	€21,159	19.1	35.5	
			Not treated	€12,113	18.7	34.7	
			Trt vs NoTrt (ICER)	**€21,069**	**per QALY**	€10,953	per LY
			Δ	**€9,046**	**0.4**	**0.8**	
				Cost	**QALYs**	**LYs**	
DC	0.132	0.099	**CHC treated**	€21,167	19.1	35.5	
			Not treated	€12,195	18.7	34.7	
			Trt vs NoTrt (ICER)	**€21,296**	**per QALY**	€11,152	per LY
			Δ	**€8,972**	**0.4**	**0.8**	
				Cost	**QALYs**	**LYs**	
HCC	0.580	0.228	**CHC treated**	€21,223	19.1	35.5	
			Not treated	€12,751	18.7	34.8	
			Trt vs NoTrt (ICER)	**€21,676**	**per QALY**	€11,688	per LY
			Δ	**€8,472**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
LT (within 1 yr)	0.129	--	**CHC treated**	€21,223	19.1	35.5	
			Not treated	€12,751	18.7	34.8	
			Trt vs NoTrt (ICER)	**€21,676**	**per QALY**	€11,688	per LY
			Δ	**€8,472**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
LT (after 1 yr)	0.033	0.033	**CHC treated**	€21,223	19.1	35.5	
			Not treated	€12,751	18.7	34.8	
			Trt vs NoTrt (ICER)	**€21,676**	**per QALY**	€11,688	**per LY**
			Δ	**€8,472**	**0.4**	**0.7**	

LHS - Cost per state			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	**LHS**		**Cost**	**QALYs**	**LYs**	
CHC	€522	€1,335	**CHC treated**	€22,790	19.1	35.5	
			Not treated	€29,238	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€16,496**	**per QALY**	-€8,895	**per LY**
			Δ	**-€6,447**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
CIRRHOSIS	€1,512	€3,464	**CHC treated**	€22,856	19.1	35.5	
			Not treated	€29,895	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€18,009**	**per QALY**	-€9,711	**per LY**
			Δ	**-€7,039**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
DC	€6,350	€8,495	**CHC treated**	€22,871	19.1	35.5	
			Not treated	€30,043	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€18,349**	**per QALY**	-€9,894	**per LY**
			Δ	**-€7,172**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	

HCC	€12,744	€9,578	**CHC treated**	€22,852	19.1	35.5	
			Not treated	€29,854	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€17,915**	**per QALY**	-€9,660	**per LY**
			Δ	**-€7,002**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
LT (within 1 yr)	€90,986	€97,635	**CHC treated**	€22,853	19.1	35.5	
			Not treated	€29,865	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€17,941**	**per QALY**	-€9,674	**per LY**
			Δ	**-€7,012**	**0.4**	**0.7**	
				Cost	**QALYs**	**LYs**	
LT (after 1 yr)	€17,612	€5,989	**CHC treated**	€22,834	19.1	35.5	
			Not treated	€29,670	18.7	34.8	
			Trt vs NoTrt (ICER)	**-€17,492**	**per QALY**	-€9,432	**per LY**
			Δ	**-€6,837**	**0.4**	**0.7**	

Table 25. Markov model for young patients treated in CIRRHOSIS status: Cortesi et al [4] versus LHS data

Cortesi et al. [4]			Results per patient (deterministic): time horizon lifetime				
Treated in CIRR state				Cost	QALYs	LYs	
(mean age=53)			CIRRHOSIS treated	€48,332	14.6	24.5	
			Not treated	€33,816	7.9	11.6	
			Trt vs NoTrt (ICER)	€2,170	per QALY	€1,134	per LY
			Δ	€14,516	6.7	12.8	
LHS - Probability Transitions			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	LHS		Cost	QALYs	LYs	
CIRRHOSIS --> DC	0.042	0.043	CIRRHOSIS treated	€48,384	14.5	24.4	
			Not treated	€33,919	7.9	11.6	
			Trt vs NoTrt (ICER)	€2,165	per QALY	€1,132	per LY
			Δ	€14,465	6.7	12.8	
				Cost	QALYs	LYs	
CIRRHOSIS --> HCC	0.033	0.042	CIRRHOSIS treated	€48,479	14.5	24.4	
			Not treated	€35,211	7.6	11.1	
			Trt vs NoTrt (ICER)	€1,908	per QALY	€1,000	per LY
			Δ	€13,268	7.0	13.3	
				Cost	QALYs	LYs	
DC --> HCC	0.058	0.040	CIRRHOSIS treated	€48,475	14.5	24.4	
			Not treated	€35,158	7.6	11.2	
			Trt vs NoTrt (ICER)	€1,927	per QALY	€1,010	per LY
			Δ	€13,316	6.9	13.2	
				Cost	QALYs	LYs	
DC --> LT	0.009	0.027	CIRRHOSIS treated	€48,691	14.5	24.4	
			Not treated	€38,045	7.7	11.3	
			Trt vs NoTrt (ICER)	€1,555	per QALY	€815	per LY
			Δ	€10,645	6.8	13.1	
				Cost	QALYs	LYs	
HCC --> LT	0.108	0.057	CIRRHOSIS treated	€47,569	14.5	24.3	
			Not treated	€34,262	7.6	11.1	
			Trt vs NoTrt (ICER)	€1,918	per QALY	€1,006	per LY
			Δ	€13,307	6.9	13.2	
LHS - Probability of Death			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	LHS		Cost	QALYs	LYs	
CIRRHOSIS	0.032	0.024	CIRRHOSIS treated	€47,913	14.6	24.4	
			Not treated	€35,729	7.9	11.7	
			Trt vs NoTrt (ICER)	€1,833	per QALY	€959	per LY
			Δ	€12,184	6.6	12.7	
				Cost	QALYs	LYs	
DECOMP.CIRRHOSIS	0.132	0.099	CIRRHOSIS treated	€48,075	14.6	24.5	
			Not treated	€37,755	8.1	12.1	
			Trt vs NoTrt (ICER)	€1,599	per QALY	€837	per LY

			Δ	€10,320	6.5	**12.3**	
				Cost	**QALYs**	**LYs**	
HCC	0.580	0.228	**CIRRHOSIS treated**	€53,164	14.9	25.1	
			Not treated	€50,577	8.9	13.4	
			Trt vs NoTrt (ICER)	**€429**	**per QALY**	€222	per LY
			Δ	€2,588	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
LT (within 1 yr)	0.129	0.129	**CIRRHOSIS treated**	€53,164	14.9	25.1	
			Not treated	€50,577	8.9	13.4	
			Trt vs NoTrt (ICER)	**€429**	**per QALY**	€222	per LY
			Δ	€2,588	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
LT (after 1 yr)	0.033	0.033	**CIRRHOSIS treated**	€53,164	14.9	25.1	
			Not treated	€50,577	8.9	13.4	
			Trt vs NoTrt (ICER)	**€429**	**per QALY**	€222	per LY
			Δ	€2,588	6.0	**11.7**	
LHS - Cost per state			**Results per patient (deterministic): time horizon lifetime**				
	Cortesi	**LHS**		**Cost**	**QALYs**	**LYs**	
CIRRHOSIS	€1,512	€3,464	**CIRRHOSIS treated**	€54,033	14.9	25.1	
			Not treated	€63,995	8.9	13.4	
			Trt vs NoTrt (ICER)	**-€1,652**	**per QALY**	-€855	per LY
			Δ	-€9,963	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
DC	€6,350	€8,495	**CIRRHOSIS treated**	€54,285	14.9	25.1	
			Not treated	€67,184	8.9	13.4	
			Trt vs NoTrt (ICER)	**-€2,139**	**per QALY**	-€1,107	per LY
			Δ	-€12,899	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
HCC	€12,744	€9,578	**CIRRHOSIS treated**	€52,576	14.9	25.1	
			Not treated	€63,444	8.9	13.4	
			Trt vs NoTrt (ICER)	**-€1,802**	**per QALY**	-€932	per LY
			Δ	-€10,868	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
LT (within 1 yr)	€90,986	€97,635	**CIRRHOSIS treated**	€52,659	14.9	25.1	
			Not treated	€63,839	8.9	13.4	
			Trt vs NoTrt (ICER)	**-€1,854**	**per QALY**	-€959	per LY
			Δ	-€11,180	6.0	**11.7**	
				Cost	**QALYs**	**LYs**	
LT after 1 yr)	€17,612	€5,989	**CIRRHOSIS treated**	**€51,241**	**14.9**	**25.1**	
			Not treated	**€57,061**	**8.9**	**13.4**	
			Trt vs NoTrt (ICER)	**-€965**	**per QALY**	-€499	per LY

	Δ	-€5,820	6.0	11.7

Table 26. Markov model for young patients treated in CHC status: Cortesi et al [4] versus LHS results, synthesis

Models	CHC Treated vs NotTreated			
	ICERs	Δ cost	QALY	LYs
Cortesi et al. [4]	€ 2,479	€ 6,702	2.7	6.9
LHS-Transition Probabilities	€ 5,367	€ 9,992	1.9	5.0
LHS-CHC vs POP mortality	€ 20,496	€ 9,100	0.9	0.9
LHS-Probability of Death	€ 21,676	€ 8,472	0.7	0.8
LHS-Costs	€ -17,492	-€ 6,837	0.7	0.8

Table 27. Markov model for young patients treated in CIRRHOSIS status: Cortesi et al [4] versus LHS data: synthesis

Models	CIRRHOSIS Treated vs NotTreated			
	ICER	Δ cost	QALY	LYs
Cortesi et al. [4]	€ 2,170	€ 14,516	6.7	12.8
LHS-Transition Probabilities	€ 1,918	€ 13,307	6.9	13.2
LHS-CHC vs POP mortality	--	--	--	--
LHS-Probability of Death	€ 429	€ 2,588	6.0	11.7
LHS-Costs	-€ 965	-€ 5,820	6.0	11.7

Table 28. Markov model for elderly patients: cost per QALY gained by age and frailty

AGE	Ciaccio et al [5]			LHS data		
	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail
65	€ 6,457	€ 7,768	€ 10,118	€ 4,017	€ 4,733	€ 6,066
70	€ 8,608	€ 10,815	€ 14,534	€ 5,147	€ 6,346	€ 8,439
75	€ 12,509	€ 16,622	€ 23,308	€ 7,298	€ 9,580	€ 13,387
80	€ 19,830	€ 28,398	**€ 42,165**	€ 11,620	€ 16,622	€ 24,848
85	€ 32,998	**€ 52,455**	**€ 84,965**	€ 20,233	€ 32,682	**€ 54,252**

Figure 17. Markov model for elderly patients: cost per QALY gained by age and frailty

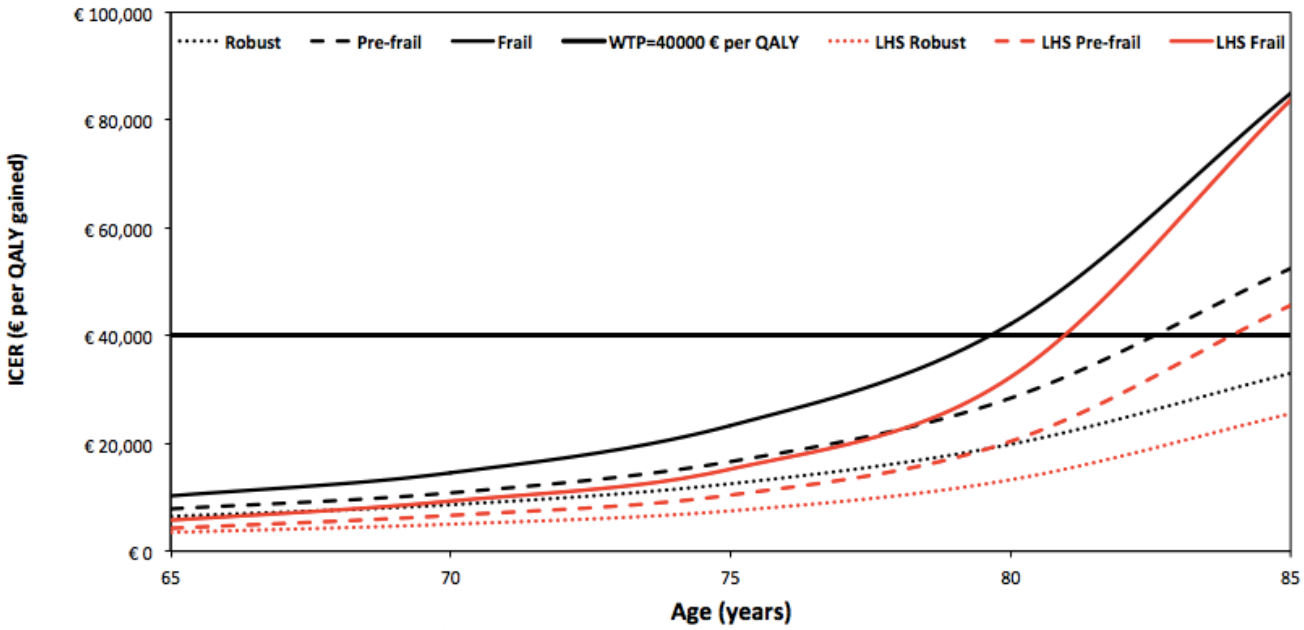


Table 29. Markov model for elderly patients: variation in cost and utility gained by age and frailty

	Robust				Pre-Frail				Frail			
	Δ cost		Δ utility		Δ cost		Δ utility		Δ cost		Δ utility	
AGE	Ciaccio	LHS	Ciaccio	LHS	Ciaccio	LHS	Ciaccio	LHS	Ciaccio	LHS	Ciaccio	LHS
65	31,056	25,476	4.81	6.34	31,462	25,561	4.05	5.40	31,872	25,743	3.15	4.24
70	31,965	25,705	3.71	4.99	32,624	26,086	3.02	4.11	33,232	26,526	2.29	3.14
75	33,526	26,784	2.68	3.67	34,465	27,564	2.07	2.88	35,275	28,327	1.51	2.12
80	35,740	28,850	1.80	2.48	36,931	30,085	1.30	1.81	37,893	31,183	0.90	1.25
85	38,381	31,957	1.16	1.58	39,736	33,573	0.76	1.03	40,759	34,897	0.48	0.64

Figure 18. Markov model for elderly patients: variation of cost and utility for robust patients by age

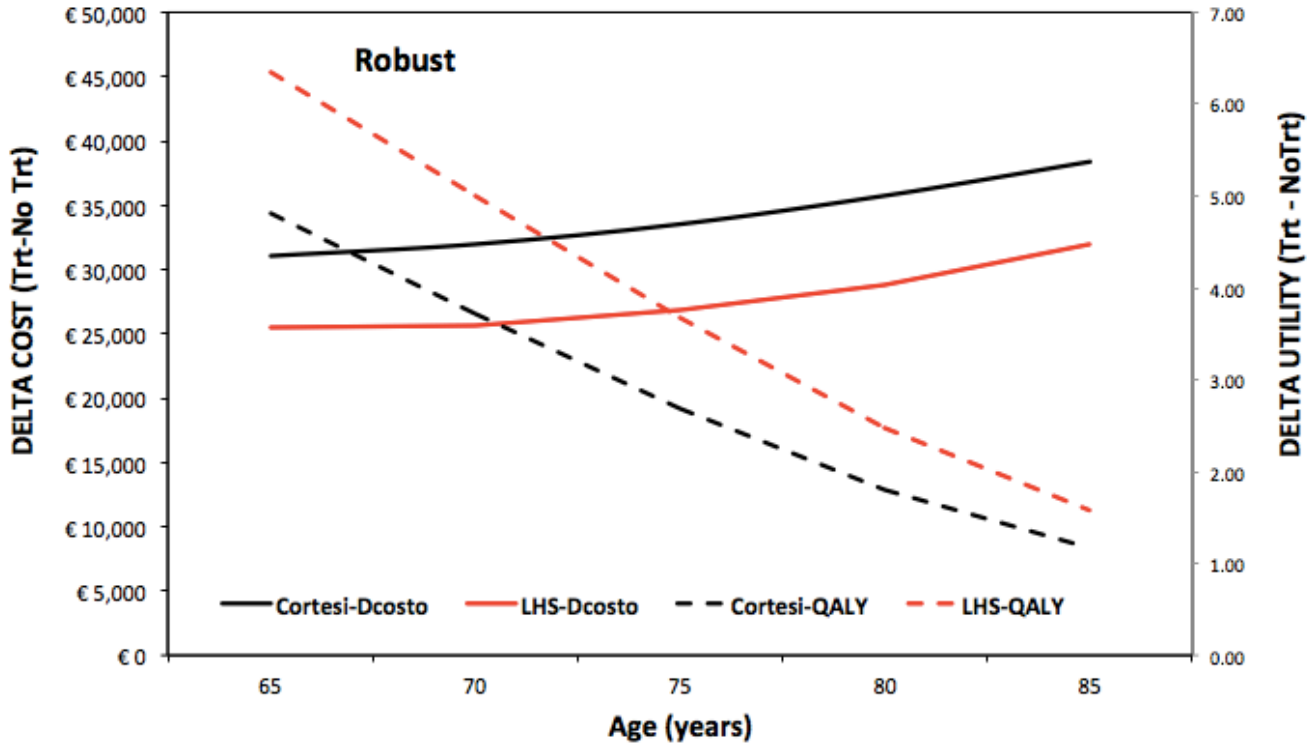


Figure 19. Markov model for elderly patients: variation of cost and utility for pre-frail patients by age

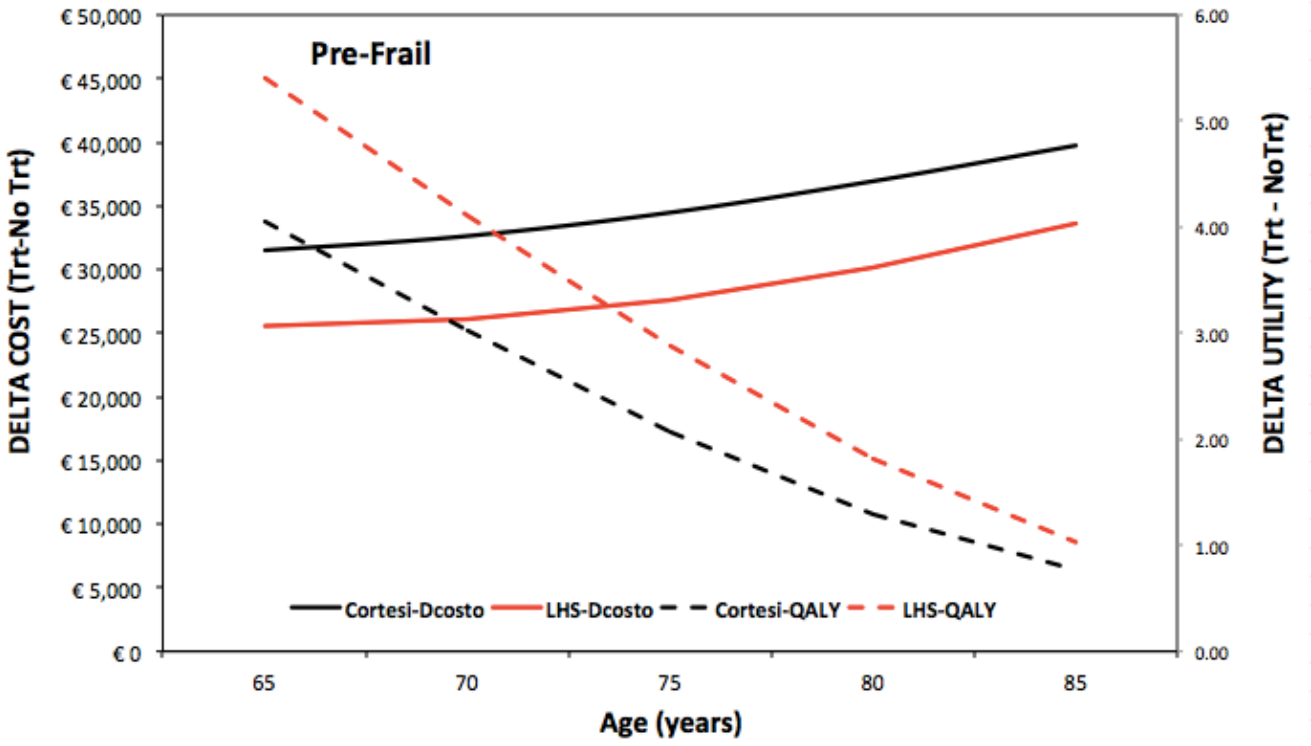
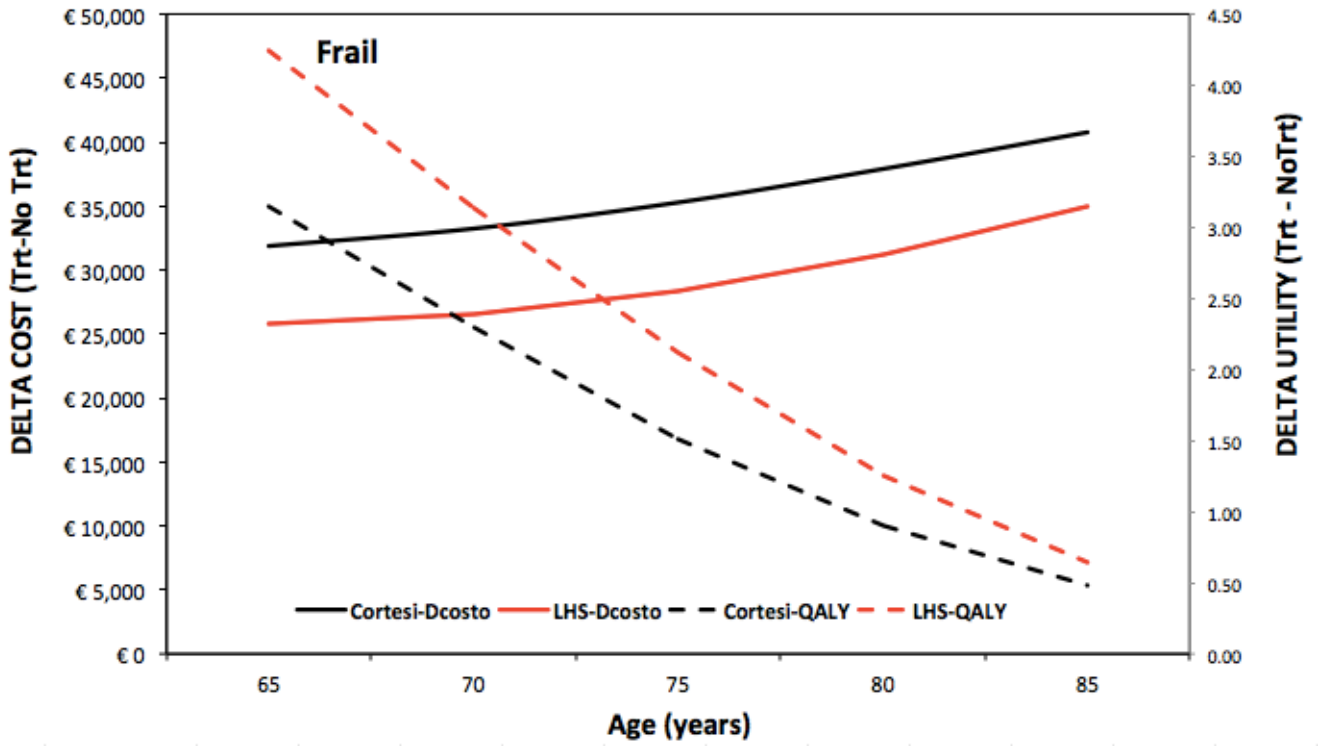


Figure 20. Markov model for elderly patients: variation of cost and utility for frail patients by age



4. Discussion

The burden of disease of patient with CHC by phase of disease progression

By the perpective of the healthcare service, the first result to consider was the prevalence of known CHC subjects among the resident population of the province of Bergamo: by the end of 2014, 9 subjects every 1,000 resulted to live with a chronic hepatic disease.

Age and comorbidity index, both elements strictly related with less healthy condition, had an increasing trend with the progression of the disease (Table 2). Other than the known condition related to liver, the most prevalent comorbidities detected on the study population where cancer and diabetes (Figure 8) that contributed in requiring services to the healthcare provider.

The results on incidence reported in paragraph 3.3 were referred to the incidence of the occurrence of new cases of CHC detected by the healthcare service (LHS) through the exemption for CHC. Every 100,000 subjects the LHS of Bergamo detected annually 69 subjects with CHC, 78 among male and 60 among females: the sex difference remained once adjusted for differences in age distribution within male and female populations. Similar results were observed by Mazzeo et al [16] who performed a study following around 1,646 adult subjects for 10 years (1986-1996) showing an incidence of 50.3 per 100,000 subjects in the Northern of Italy.

As expected, the survival analysis by state of disease (**Table 8**-**Table 12**) showed and increasing trend in mortality rates with the progression of disease and the age class. In this context we compared the mortality of the study population in CHC state of disease with respect to the mortality of the source population. The comparison was performed since Cortesi et al [4] considered the mortality of CHC patients higher than the ones of the general population refferring to the mortality rate ratio reported by El-Kamary et al [17]: 1.79 (0.83–3.88). According to our estimation, performed by age and sex-standardized mortality rates, there is no excess of mortality for CHC patients (even the not treated ones) with respect to the source population (Table 6, **Table 7**, **Table 14**).

Another interesting aspect from the above results was represented by the quote of the CHC patients who had no prescription of PEG-IFNα and ribavirin: this quote was 53% of the entire study population. The mean age of the not treated study population was slighlty higher that the treated study population (49 years versus 47, data not reported in the present paper) and no differences in terms of cci score. According to the COME study [18], that collected 1,088 patients with CLDs in two hospitals of Bergamo and Naples, among those patients with CHC etiology only 12% received an antiviral treatment.

The progression of disease expressed by rates per 1,000 person-years (Table 15-Table 19), indicated that progression increased with the increasing of age: we cannot say from the present data if the age worked in accelerating the progression of disease or if elderly patients were detected by the LHS in a fibrosis advanced stage. It is important to remember that fibrosis stage is not traceable by administrative data and all patients in CHC state of disease have in reality different fibrosis condition. This aspect will discuss later in the paper. The transposition of the progression of disease rates into transition probabilities was given in Table 20-Table 21. The effect of age on the progression of disease discussed earlier was expressed here in the less quote of elderly patients that remained in the state of disease without progression: 99.3% and 97.9% remained in CHC state respectively when aged 15-64 and over 65, 89.1% and 82.5% remained in CIRRHOSIS state respectively when aged 15-64 and over 65, 83.5% and 74.0% remained in DECOMPENSATED CIRRHOSIS state respectively when aged 15-64 and over 65. We cannot replicate the above comparison for the HCC state because for elderly patient the model do not consider the LT state in line with the clinical practice.

Considering the entire study population (treated and not treated CHC patients), the trend of costs was increasing with the progression of disease, for both age classes (Table 22 and Figure 15). The highest level of cost was reported for the LT state because it considered the cost for the surgical intervention of transplantation that was around 70,000€. After 1 year from the liver transplantation the mean cost per patient per year decreased under 20 thousand euros. Comparable results were showed by the COME study [18]: 1,920€ per year per patient in CHC state of disease, 4,368€ in CIRRHOSIS (with no distinction between cirrhosis and decompensated cirrhosis), 14,088€ in HCC, 42,504€ in LT.

The mean costs per patients of the not treated study population, those involved in the Markov models, were sligthly lower in CHC state of disease with respect to the entire study population (1,490 versus 2,230): the difference was mainly attributable to the absence of IFN cost.

Markov model for young patients treated in CHC state of disease

Once the Markov model of Cortesi et al [4] was modified to be suitable to LHS data, the main result was the one reported in

Table 24. The result can be interpreted as follows: treating patients in CHC state of disease using DAAs costs on average 21,420€ per patient for his/her lifetime and it allowed to obtain 18.8 QALYs (life years adjusted for quality) and 34.8 LYs (life years); not treating patients in CHC state of disease costs on average 14,718€ per patient for his/her lifetime and it allowed to obtain 16.1 QALYs (life years adjusted for quality) and 27.9 LYs (life years). Using the ICER, that is given by the cost difference between treatment and not treatment over the QALY difference between treatment and not treatment, the result can be interpreted as

follows: treating patients in CHC state of disease using DAAs allowed to gain 1 QALY for 2,479€, that is much lower than the standard threshold of 40,000€ per QALY commonly used to define a treatment as a cost-effective treatment [4]. The DAAs treatment resulted to be cost-effective because with a relative small difference of euros (6,702€) allowed to gain 2.7 QALYs and 6.9 LYs.

When we changed the transition probabilities from CHC to CIRRHOSIS state (from 0.014 used by Cortesi et al [4] to 0.0027 estimated by LHS data) the DAAs remaind cost-effective but the Δcost increase: this was because according to LHS estimation patients in cirrhosis state will be fewer and so the cost of managing them will be lower. Moreover the ΔQALY decrease because cirrhosis patients will be fewer than before, not reducing the QALY with their utility that was lower than the ones of CHC state.

Changing the other transition probabilities did not modify significantly the ICER that was now equal to 5,367€ per QALY gained.

A big change in ICER happend when we modified the excess mortality used by Cortesi et al [4] from a mortality relative rate of 1.79 to 1, as resulted by our estimation. Since the DAAs did not reduce mortality in CHC state, the LYs and the QALYs become more or less the same between two treatment options and the effect of the ICER was 20,496€ per one QALY gained.

Changing the probability of deaths for the other states of disease did not modify significantly the ICER, that was now equal to 21,676€ per QALY gained.

The mean cost per patient per year that we estimated using the administrative data from LHS were higher than those used by Cortesi et al [4], expecially for the CHC and cirrhosis states of disease. By construction, putting the LHS estimation of costs into the model did not have effect on the QALY nor on the LY, but it worked on costs of not treated patients that became higher than the cost of treated ones. Indeed, the DAAs treatment avoided those states that were more expensive and the final result was an ICER of -17,491€ per QALY gained: treating patients is more effective than not treating them because of cost reasoning and not for advantages in terms of QALYs gained. The Markov model populated with LHS data in the hypothesis of DAAs treatment for patients in CHC state of disease was not able to describe

the advantage in terms of QALYs and LYs. We than decided to make the hypothesis of treat patients in cirrhosis state of disease, suspecting that LHS data were not well suited to describe the CHC disease state.

Markov model for young patients treated in CIRRHOSIS state of disease

Consider now the hypothesis of treating patients when they are in cirrhosis state of disease (

Table 25).

Once the Markov model of Cortesi et al [4] was modified to consider the above hypothesis of treatment, the result can be interpreted as follows: treating patients in CIRRHOSIS state of disease using DAAs costs on average 48,332€ per patient for his/her lifetime and it allowed to obtain 14.6 QALYs (life years adjusted for quality) and 24.5 LYs (life years); not treating patients in CIRRHOSIS state of disease costs on average 33,816€ per patient for his/her lifetime and it allowed to obtain 7.9 QALYs (life years adjusted for quality) and 11.6 LYs (life years). Using the ICER, the result can be interpreted as follows: treating patients in CIRRHOSIS state of disease using DAAs allowed to gain 1 QALY for 2,170€, again an estimation that is much lower to the standard threshold of 40,000€ per QALY.

When we changed the transition probabilities using the LHS data, the ICER did not change much. It slightly changed with the modification of the probabilities of death: those estimated by the LHS data were lower than those used by Cortesi et al [4] resulting in lower values of LYs and QALYs gained. Indeed the treatment should avoid a lower number of life years lost for death with respect to those avoided with original probability of mortality: after those changes the Δcost was 2,588€, the ΔQALY was 6.0 and the ΔLY was 11.7.

Using the cost estimation based on LHS data did not affect QALYs nor LYs, buti t increased the cost of not treated patients: the advanced states of the disease were more expensive and the treatment allowed avoiding those costs.

The final ICER was equal to a -9,65€ per QALY gained: treating patients is more cost-effective than not treating them because of cost saving and because treatment allowed gaining 6.0 QALYs and 11.7 LYs.

The two hypothesis used to populate the Markov model for young patients, treating them in CHC or CIRRHOSIS state, lead us to the same conclusion of the original model: DAAs was cost-effective with respect to not treat them at all. It is important to stress that in the first hypothesis the model was not able to represent the well known positive effect of DAAs treatment in QALY and LYs.

Markov model for elderly

The Markov model for elderly proposed by Ciaccio et al [5] considered patients aged over 65 years old and characterized them using three levels of frailty: robust, pre-frail and frail. The model also considered 5 level of ages: 65, 70, 75, 80 and 85. The model was structured to obtain a cost-effectiveness evaluation of DAAs treatment on 15 patient's profiles given by the 3 levels of frailty for each of the 5 levels of age. Given the effects of the missing information related to fibrosis stage in the LHS data, we decided to perform the estimation of cost-effectiveness of treating elderly patients with DAAs from the cirrhosis state of disease. Once the Markov model of Ciaccio et al [5] was modified to be suitable to LHS data, the resulting ICERs by frailty and age levels were reported in Table 28.

The ICERs estimated using the LHS data were concordant with the original ones: treating elderly patients in cirrhosis state with DAAs was cost-effective with respect to no treatment for almost every patient's profile. While the original model for elderly determined 3 ICERs higher than the williness to pay of 40,000€ per QALY (in frail patients aged 80 and 85 and in pre-frail patients aged 80 years old), the model populated by the LHS data was over that threshold only for frail patients aged 85 years old. A graphycal description of the 15 ICERs was in Figure 20. As already said, the ICER estimated using LHS data were concordant in trend with respect to the ICERs estimated by Ciaccio et al [5], but those estimated with the LHS data remained lower than the others. The main reason of that result was the fact that with administrative data we could evaluate costs related to patients aged over 65 years old, while no published references were available for Ciaccio et al [5], indeed they used the estimation of Cortesi et al [4] for costs. Since the LHS cost estimations were higher that the

ones used by Cortesi et al [4] the DAAs treatment resulted less expensive since avoided the advanced disease states.

Table 29 described for the 15 patient's profiles the two element determining the ICERs of **Figure 11**: the differential in cost and in utility. For each patient's profile the incremental cost of Ciaccio et al [5] was higher that the ones estimated by LHS data: the cost of treatment did not change between Ciaccio and LHS, but the distance between the cost of treatment and the cost of disease state was higher where the cost of the disease state was lower, that is to say in Ciaccio et al [5] estimation. On the other hand, assigning higher costs to the disease state (as the estimation with LHS data did) imposed that the treatment avoid higher costs and the distance between treatment and not treatment was lower.

Regarding the differential in utility, LHS data estimated transition probabilities slightly higher than the ones used by Ciaccio et al [5]: from cirrhosis to decompensated cirrhosis LHS data estimated a transition probability of 0.07 versus 0.056 by Ciaccio et al [5], from cirrhosis to HCC 0.056 versus 0.054, and from decompensated cirrhosis to HCC 0.045 versus 0.063. Simulating more patients in advancend state of disease allowed the treatment to gain higher utility, resulting in a higher differential utility than Ciaccio et al [5].

Similarly to the transition probabilities was the probability to death reasoning. Respectively the probability of death in LHS and Ciaccio et al [5] were: 0.049 and 0.0093 in cirrhosis state; 0.216 and 0.132 in decompensated cirrhosis state; 0.196 and 0.427 in HCC state. Again, the LHS estimations allowed the treatment to avoid more deaths and gain higher utility, resulting in a higher differential utility than Ciaccio et al [5].

Figure 18-**Figure 20** showed graphically the common trend of differential in cost and utility by patient's profile obtained by the two estimations of Ciaccio et al [5] and of LHS.

5. Conclusions

Even if the estimation of the results made on LHS data followed the same direction of the original models, some considerations should be done.

First, one limit of the present work was the absence of a gold standard to validate the selection algorithm of the study population. When we started the project we thought to link the LHS data with the VBMH ones [19]. The latter study, on which the utility values used by all the estimation in the present analysis was based, has been collecting clinical data on CLDs since 2013, involving one of the most important hospital of the Province of Bergamo. Unfortunately the data were not structured to perform a probabilistic record linkage between the two sources, VBMH and LHS.

Second, administrative data did not give clinical information on fibrosis stage. This element could be determinant in defining the progression of disease from CHC to CIRRHOSIS and it was one of the two elements that deleted the treatment advantages in terms of LYs and QALYs in young model. Once we passed over this state of disease and we considered the CIRRHOSIS state, the transition probabilities mantained the final result stable in terms of costs and effectiveness.

The other element that deeply modified the results was the evidence of no excess of mortality for CHC patients with respect to the general population. We verified this evidence by the estimation of SMRs using the LHS data, but we cannot demostrate that this should be generalizable in other populations.

The limitations of the administrative data in relation of the missing information on fibrosis stage can be replicated in the elderly model, but once we assessed it in the young patients model we considered the hypothesis of treatment from cirrhosis state of disease.

The scarse available literature on the issue of elderly CHC patients could be filled by estimations performed on administrative data. These data were not build for reasearch purposes, but they were reliable for the evaluation of direct healthcare costs according to the healthcare provider perspective. Moreover for some disease, as in example the chronic liver disease, the progression of the pathology was traceable using administrative flows, as HDs

or exemptions. Since decision-analytical models are becoming more and more important in the evaluation of healthcare interventions, researchers should be able to access administrative data collected on regional and national level in order to perform population-based estimations.

6. Appendix

Table 30. Exclusion criteria for the study population

Diagnosis	Exemption codes and description
CHRONIC HEPATITIS and no prescriptions of ribavirina (ATC J05AB04)	**016.070.9** Unspecified viral hepatitis without mention of hepatic coma **AND** **No prescription of ribavirin (ATC** J05AB04)
HBV	**016.070.32** Chronic viral hepatitis B, without mention of hepatic coma, without mention of delta hepatitis **016.070.33** Chronic viral hepatitis B, without mention of hepatic coma, with mention of delta hepatitis
HEMOCHROMATOSIS	**RCG100**
PRIMARY SCLEROSING CHONALGITIS	**RI0050**
POLYCYSTIC LIVER DISEASE	**RN0230**
ALCOHOLIC CIRRHOSIS	**008.571.2**
PRIMARY BILIARY CIRRHOSIS	**008.571.6**
WAITING LIST FOR LIVER TRANSPLANTATION	**050**
LIVER TRANSPLANTATION	**052.V42.7**
Diagnosis	**ICD-9 codes from HDs diagnosis fields**
HBV	**070.2X** Viral hepatitis B with hepatic coma **070.3X** Viral hepatitis B without mention of hepatic coma
AUTOIMMUNE HEPATITIS	**571.42** Autoimmune Hepatitis
Diagnosis	**Active ingredient and ATC code of drugs specific for HBV treatment**
HBV	

Table 31. ICD-9 codes from HDs diagnosis/procedures fields for progression of disease detection

Diagnosis	ICD-9 codes from HDs diagnosis/procedure fields
CIRRHOSIS	**571.2** Chronic liver disease and cirrhosis
	571.5 Cirrhosis of liver without mention of alcohol
	456.1x esophageal varices without bleeding
DECOMPENSATED CIRRHOSIS	**456.0x** esophageal varices with bleeding
	567.23 peritonite batterica spontanea
	789.5x ascites
	572.2x, 348.3x hepatic coma/encephalopathy or unspecified encephalopathy
	572.3 hepatorenal syndrome
	572.4 portal hypertension
	576.2 ittero ostruttivo senza calcolosi
HCC	**155.0x** Malignant neoplasm of liver, primary
	155.1 colangiocarcinoma
	156.1 colangiocarcinoma
Liver Transplantation	**V42.7** fegato sostituito da trapianto
	50.51 (in procedure field)
	50.59 (in procedure field)

Table 32. Estimation of transition probabilities

CHC->CIRRHOSIS	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.0027	0.0042	0.0027	0.0037	0.0042
65+	0.0086	0.0148	0.0086	0.0130	0.0148
CHC-DECOMP	**KM rates**	**weibull**	**exp**	**gompertz**	**log-logistic**
15-64	0.0014	0.0019	0.0014	0.0015	0.0019
65+	0.0044	0.0032	0.0044	0.0035	0.0032
CHC-Dx	**KM rates**	**weibull**	**exp**	**gompertz**	**log-logistic**
15-64	0.0026	0.0024	0.0026	0.0032	0.0024
65+	0.0076	0.0055	0.0076	0.0079	0.0054
CIRR-DECOMP	**KM rates**	**weibull**	**exp**	**gompertz**	**log-logistic**
15-64	0.044	0.0767	0.0433	0.0770	0.0779
65+	0.073	0.1045	0.0700	0.1046	0.1074

CIRR-HCC	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.043	0.0801	0.0417	0.0554	0.0815
65+	0.058	0.1157	0.0559	0.1102	0.1188
CIRR-Dx	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.024	0.0488	0.0236	0.0328	0.0494
65+	0.050	0.1029	0.0488	0.1095	0.1055
DECOMP-HCC	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.041	0.0568	0.0399	0.0681	0.0573
65+	0.046	0.0451	0.0445	0.0481	0.0456
DECOMP-Tx	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.027	0.0436	0.0268	0.0624	0.0442
65+	0.000	--	--	--	--
DECOMP-Dx	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.104	0.1232	0.0987	0.1363	0.1242
65+	0.243	0.2763	0.2157	0.2888	0.2920
HCC-Tx	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.058	0.0754	0.0566	0.1097	0.0769
65+	0.000	--	--	--	--
HCC-Dx	KM rates	weibull	exp	gompertz	log-logistic
15-64	0.210	0.2173	0.1892	0.1594	0.2279
65+	0.218	0.2740	0.1956	0.2687	0.2895
Tx-Dx	KM rates	weibull	exp	gompertz	log-logistic
15-64	30.976	--	0.0000	--	--
65+	0.000	--	--	--	--
Tx-Dx entro 1 y	KM rates	weibull	exp	gompertz	log-logistic
15-64	62.500	--	0.0606	--	--
65+	0.000	--	--	--	--

Values in yellow indicated the estimations used in populating the models

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