Seth Shaffer

Project Title: Outcome of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphomas (DLBCL) that are receiving upfront therapy in the hospital setting compared with patients diagnosed and treated in the outpatient setting

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Summary:

Study Aim: To establish the characteristics of patients with DLBCL that requires up-front in-hospital therapy, as well as their outcome post-therapy. Comparison of characteristics and outcomes with a concurrent cohort of outpatient managed group was made.
Methods: Retrospective chart review over 5 years for newly diagnosed patients with DLBCL admitted to a teaching hospital and concurrently for patients that were managed as outpatients. The study included 46 in-patients and 96 outpatients. Patients considered eligible for R-CHOP were those from age 18-80, as patients above age 81 were initially not eligible to receive Rituximab.
Results: There were 38 in-patients eligible to receive R-CHOP, with 28 receiving R-CHOP, 3 R-CVP and 7 palliation. There were 77 outpatients eligible to receive R-CHOP, with 64 receiving R-CHOP, 12 R-CVP and 1 palliation. Patients with higher IPI (3 or more) correlated with a higher need for hospitalization ($p<0.001$). Patients from rural setting were also more likely to be hospitalized ($p=0.043$). Overall survival post-diagnosis for patients eligible to receive R-CHOP was lower for in-patients compared to the outpatient group ($p=0.0002$). At 3 years the overall survival was 60.5% for in-patients and 77.7% for outpatients. There was no significant difference in survival between in-patients and outpatients that completed R-CHOP treatment ($p=0.1120$). For patients with IPI of 3 or higher that completed therapy no significant difference in survival between treatment groups was noted ($p=0.53$).
Conclusions: In-hospital patients with DLBCL eligible to receive R-CHOP had inferior outcomes compared with the outpatient group. Comparing patients that completed chemotherapy from either group, no survival differences were seen. Same applies to patients that finish therapy and have high IPI. Ability to complete R-CHOP chemotherapy in due time led to similar outcomes for either group.

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Student's Signature **Supervisor's Signature**

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Introduction

Lymphoid tissue neoplasms are the 5th most common malignancies in Canada. They are comprised of: non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, multiple myeloma, and acute and chronic lymphocytic leukemia [1]. The etiologies of lymphoid neoplasms remain largely unknown, although some risk factors have been elucidated; these include: infections with Epstein-Barr virus as well as Helicobacter pylori bacteria, and immunosuppressive disorders inherited or acquired [1].

Non-Hodgkin's lymphoma (NHL) is the most common lymphoid malignancy and is comprised of a large subset of disorders that have a different morphologic, molecular and biologic behavior. Based on their clinical behavior NHLs are classified clinically as: very aggressive, with rapid clinical progression and rapid need for intervention, aggressive lymphoma, with a moderate growth but equal need for early treatment, and indolent lymphomas, that grow more insidiously, give minimal symptoms until they reach advanced stages, and need therapy only when symptoms occur.

Diffuse large B-cell lymphoma (DLBCL) is the most common subset of NHL, an aggressive type of NHL with an incidence of 35-40% [1]. It accounts for approximately 80% of aggressive lymphomas [2]. DLBCL presents with localized disease (stage I or II) in forty percent of cases, while the remainder have extensive disease (stage III or IV) [3]. Typical presentation for a patient with DLBCL is rapidly enlarging lymph node(s), as well as exhibiting systemic symptoms (30%) such as, night sweats, unexplained weight loss, and fever or chills, symptoms defined as B-symptoms [3].

The diagnosis of DLBCL is generally made on the basis of an excised lymph node on which detailed histology as well as thorough ancillary studies are performed. These include: immunohistochemistry, flow cytometry that are using specific monoclonal antibodies: CD45, CD20, CD19, CD10, CD5 and molecular markers [4]. The detailed use of the above diagnostic methods have become necessary to differentiate a large subset of about 40 NHL's subtypes, each exhibiting specific diagnostic markers as well as specific clinical behavior.

After establishing an accurate pathologic diagnosis it is imperative to determine the extent of the disease as this has an important prognostic value in the patient's outcome. Tumor staging of patients with aggressive NHL currently uses the Ann Arbor classification [5]. To determine clinical stage (from I-IV) patients require a detailed clinical examination, as well as a complete imaging evaluation, that includes computed tomography scans (CT) of the neck, chest, abdomen and pelvis [4]. A bone marrow aspirate and biopsy is also necessary to determine the extent of the lymphoma [4]. Positron emission tomography (PET) scans have been more recently introduced and are used for disease staging and response assessment, but remains at this point an experimental instrument [4]. Prior to the initiation of treatment, cardiac function is also determined, to establish if they have a cardiac contraindication to therapy [6].

Over the past 10 years, the treatment of patients with DLBCL has seen significant improvement [7]. Until 2002, the standard management of patients with DLBCL was CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) [8], and attempts to

improve outcomes with more intensive chemotherapy did not show any further benefits [9]. The addition of Rituximab®, a monoclonal antibody for a specific B-cell antigen (anti-CD20 antigen) that causes B-cell death through various mechanisms, to CHOP chemotherapy was shown to improve all major outcomes measured in patients with DLBCL; in particular, overall survival. [1,6,10,11]. The benefit with the addition of Rituximab showed an improvement in the cure rate over 5 years of the patient population being studied of 58% vs. 45% (p=0.007) [10]. Henceforth, R-CHOP became the standard treatment for patients with DLBCL.

While R-CHOP is the standard regimen for patients with DLBCL, some patients are not able to tolerate it due to other co-existing co-morbidities. Patients with cardiac disease are unable to tolerate the use of an anthracycline (doxorubicin) since it is toxic to cardiac cells [12]. Such patients receive instead abbreviated chemotherapy regimens such as R-CVP (Rituximab, cyclophosphamide, vincristine, and prednisone), which is less effective than R-CHOP.

The outcome of patients with DLBCL treated with R-CHOP can be assessed clinically using the International Prognostic Index (IPI), which uses clinically defined prognostic factors [13,14]. The main components of the IPI are: age (>60), performance status (ECOG performance status of ≥2), presence of more than one extra-nodal site, advanced disease (stage III or IV), and elevated lactate dehydrogenase (LDH) levels above normal levels [14]. Performance status is based on the Eastern Co-operative Group Scale [15]. Based upon the IPI, patients with DLBCL with no risk factors when treated with mainstay treatment, have a 4-year survival of 94%, compared to a low of 55% for patients with 3 or more risk factors [14].

The incidence of lymphomas in Manitoba is estimated to be at 264 cases per year (CCMB Epidemiology Report 2006), with 40.0% of those being DLBCL; thus the incidence of DLBCL is approximately 105 cases/year. The majority of these patients will have received treatment in the outpatient setting, with a minority requiring hospital admission for either diagnosis, management or both. It is suspected that these patients with DLBCL are admitted to hospital due to advanced disease and symptoms, or due to associated co-morbid conditions, poorer performance status, or other issues. Data on this subset of patients as well as their outcome is not well defined. While it is assumed that patients with DLBCL who require hospital admission for their initial work-up and management tend to have poorer outcomes compared to patients treated in the outpatient setting, there is insufficient data to confirm or disprove this fact. The aim of this study is to look at the characteristics of these patients, determine the ability of these patients to be treated with standard therapy (R-CHOP), and attempts to establish their outcome. In-patients' treatment outcomes will be compared with a group of patients treated in the outpatient setting, concurrently, with R-CHOP chemotherapy.

Methods

Sample

A retrospective chart review was conducted for patients newly diagnosed with DLBCL, over a five year period, from January 2005 to December 2009, who were treated either in hospital, at Health Sciences Center (HSC), or in the outpatient setting, at CancerCare Manitoba (CCMB). These dates were chosen to correspond with the introduction of Rituximab to chemotherapy in the management of patients with DLBCL. Prior to that date patients were

managed commonly with chemotherapy only regimens (CHOP). Patients with CNS lymphoma were excluded because of different types of therapies and outcomes.

During the selected period of evaluation all subsequent in-patients were enrolled in the study. A group of subsequent patients with DLBCL managed in the outpatient setting in the same period were also selected, to compare their outcomes with the in-patient group.

Because patients over the age of 80 were initially, based on institutional guidelines ineligible to receive R-CHOP therapy, we restricted our analysis to patients 80 and younger, that were eligible to receive R-CHOP and actually received it; we will refer to this group as "R-CHOP cohort".

Variables

The variables collected were: age, gender, postal code, date of hospital admission (for in-hospital patients), date of diagnosis (coincides with the date of biopsy), clinical stage at diagnosis, presence or absence of B symptoms, ECOG performance status, and major co-morbidities of patients. IPI was collected from the chart or, when not available, was derived based on data collected. Variables related to therapy were: date of treatment initiation, type of treatment given, the date when intended treatment was completed and date of discharge from hospital (for in-hospital patients). Date of last follow-up and the day of death were also collected.

Analysis

Logistic regression was used to identify predictors of treatment location (in-patients vs. outpatients) for newly diagnosed patients with DLBCL who received R-CHOP. Predictor variables were: age, gender, residence, and IPI.

Chi-square and t-test were used to test the relationship between variables and treatment completion after therapy initiation. Variables selected were: treatment location, age, gender, residence, and IPI.

Kaplan-Meier curves were used to look at how treatment-location and treatment completion relate to survival. In addition, in-patients and outpatients survival with similar IPI was compared.

Results

Sample Characteristics

The study cohort included 46 in-patients and 96 outpatients (see Table 1). The mean age of the in-patient population was 68.3 (SD=14.2); while for the outpatient group it was 65.2 (SD=15.3). The in-patient group was comprised of 47.8% female, with the outpatient having 52.1%. Fifty percent of the in-patient group came from a rural residence, while only 28.1% of the outpatient group was from a rural residence.

Of the 46 in-patients, 28 (60.9%) received R-CHOP, 4 (8.7%) received an alternate form of chemotherapy (R-CVP), and 14 (30.4%) received no chemotherapy. There were 38 in-patients

that were 80 and younger and therefore eligible to receive R-CHOP. Of these 38 in-patients, 28 received R-CHOP, 3 received R-CVP, and 7 received palliation.

Of the 96 outpatients, 69 (71.9%) received R-CHOP, 18 (18.8%) received an alternate form of chemotherapy (R-CVP), and 9 (9.4%) received no chemotherapy. There were 77 patients in the outpatient setting who were ages 80 and younger and therefore eligible to receive R-CHOP. Of these 77 outpatients, 64 received R-CHOP, 12 received R-CVP and 1 received palliation.

Of the in-patient group 21.7% had a favorable IPI (0-2), compared with 70.8% of the outpatient population. Within the R-CHOP cohort, 28.6% had a favorable IPI in the in-patient group and 75% had a favorable IPI in the outpatient group.

Hospital admission predictors

Patients with an IPI of 3 or higher at diagnosis were significantly more likely to require hospital admission for initial management [Odds ratio (OR) = 8.426; p-value <0.001]. Patients from a rural setting were more likely to be hospitalized compared to those who resided in Winnipeg [OR = 2.335; p-value = 0.0431]. Patients with an IPI of 3 or greater from the R-CHOP cohort were also more likely [OR = 7.012; p-value = 0.0002] to be admitted to hospital, compared to patients with a more favorable IPI (0-2). From the same R-CHOP cohort, those from a rural setting were more likely, but not significantly, to be admitted to hospital for initial treatment [OR = 2.362; p-value = 0.0941].

In-patients received treatment sooner relative to the outpatients, but also more in-patients died prior to receiving R-CHOP or an alternate management (Figure 1). At one month post-diagnosis 71.1% of in-patients had been treated, while only 18.2% of outpatients received therapy. At three months post-diagnosis, 81.6% of inpatients have been treated versus 79.2% of the outpatients. However, in-patients were more likely to die prior to receiving therapy: 7.9% and 15.8% respectively, at one and three months, compared with no deaths occurring in the outpatient group at the same intervals.

Predictors of treatment completion

No variables were significantly predictive of treatment completion (treatment location, gender, residence or IPI; see Table 2). The average age of those who did not complete treatment was 62.3 (SD=12.6), while the average age of those who did complete treatment was 59.7 (SD=13.0). In the in-patient setting, 7 of 28 (25.0%) were unable to complete treatment, while in the outpatient setting, 9 of 64 (14.1%) were unable to complete their treatment.

Survival

Overall survival post-diagnosis for all patients 80 and younger who were eligible to receive R-CHOP was lower for the in-patient group as compared to the outpatient group (p-value = 0.0002) (Figure 2). At 1 year post-diagnosis for in-patients who were eligible for R-CHOP, the overall survival was 60.5%, while it was 92.2% for the outpatients. At three years post-diagnosis, overall survival for in-patients was 46.9% and 77.7% for outpatients.

Survival post-diagnosis for the R-CHOP cohort was lower among in-patients than outpatients (p-value = 0.0224) (Figure 3). At 1 year post-diagnosis for the R-CHOP cohort, overall survival for the in-patients was 71.4%, compared with 90.6% for the outpatients. At three year post-diagnosis, survival for the in-patient group was 57.7%, compared to 78.2% for the outpatient group.

There was no significant difference in survival between in-patients and outpatients who completed treatment (defined as 15 weeks post-treatment initiation) (p-value = 0.1120). Survival was calculated after the 15-weeks post-treatment initiation. Survival at one-year for in-patients that completed therapy was 75.9% and 60.0% for those in-patients who did initiate but did not complete treatment. For outpatients that completed therapy the one-year survival was 92.0% and 41.7% for those who did not. Two-year survival for in-patients that completed treatment was 75.9%, while for outpatients it was 86.7%; for those that did not complete therapy, survival was 40.0% for in-patients, and 41.7% for outpatients.

For patients with a poor IPI (3 or greater), who were treated with R-CHOP and completed therapy (Figure 4), there was no significant difference in survival between treatment groups (p-value = 0.5298). Overall survival at one year for the in-patients was 68.2%, and for outpatients it was 69.2%. At two years, survival for in-patients with an IPI of 3 or greater was at 68.2% while for outpatients it was 60.6%. Further, for patients that completed therapy and had a good IPI (0-2), there was again no significant difference between treatment groups (p-value = 0.0710). Overall survival at one year for both in-patients and outpatients with a good IPI was 100%. At two years, overall survival remained at 100% for in-patients, and was 94.9% for outpatients.

When assessing time-to-treatment for both groups of patients, the in-patient group with a poor IPI (3 or greater) had a significantly shorter time-to-treatment interval from the point of diagnosis compared with the outpatient group (18.3 days vs. 75.5 days; p-value = 0.0003). For those with a good IPI (0-2), in-patients had a shorter time-to-treatment interval from the point of diagnosis, albeit non-significantly, as compared to the outpatients (28.6 days vs. 58.6 days; p-value = 0.0725).

Discussion

DLBCL is an aggressive NHL subtype that requires rapid diagnosis, staging and management. This is performed most commonly in the outpatient setting and most patients receive either immuno-chemotherapy (R-CHOP) or a combination of immuno-chemotherapy and involved field radiotherapy. Due to potential toxicities of immuno-chemotherapy with R-CHOP, therapy is indicated for patients of age 18 to 80. Patients' outcomes depend on multiple factors, with the most pertinent being: age, ability to undertake the immuno-chemotherapy, performance status, cardiac and hepatic status, and others. Only a minority of patients actually do require hospital admission for urgent diagnosis and/or management; this is mainly due to a rapidly advancing disease, significant associated symptoms, older age, associated co-morbidities that complicate patient`s management, geographical distance from the treatment centre, and others. Our study evaluated a cohort of 46 patients with DLBCL admitted in a teaching hospital over a period of 60 months analyzing their demographics, their ability to receive therapy or any form of management, and also determined their outcome. A comparison group of 96 patients managed

contemporaneously in the outpatient setting were also analyzed to compare survival outcomes with the in-patient group.

Despite the fact that the in-patients showed poorer prognostic indicators at diagnosis, the treatment rate for this group (73.7%) did not significantly differ from that of the outpatients group (83.1%). While our data shows that a majority of patients from both groups eligible for R-CHOP received predominantly R-CHOP therapy, some were managed with R-CVP. A thorough analysis about why patients received R-CVP versus R-CHOP was not performed, but a cursory review showed that some patients had cardiac conditions that did not allow the administration of an anthracycline, others had poor performance status, or had associated co-morbidities.

The IPI risk score was, not un-expectantly, higher in the in-patient group (advanced stage, poor performance status, etc.) and a high IPI predicted an increased likelihood of requiring in-patient therapy. The same was true in the R-CHOP cohort of treated patients; a high IPI conferred an increased risk for hospital admission, compared to patients with a more favorable IPI (0-2). As anticipated, patients coming from a rural setting were more likely to be hospitalized compared to those who reside in Winnipeg. When looking at just the R-CHOP cohort, however, those from a rural setting were non-significantly more likely to be admitted to hospital for initial treatment – which is due to the small sample size.

In-patients were more likely to receive treatment sooner than outpatients, but simultaneously were at higher risk of dying shortly post-diagnosis, because of inability to be treated with standard therapy for various reasons mentioned above. Within the first three months post-diagnosis, no outpatients had died, yet the same cannot be said of the in-patient group.

Once treatment was initiated though, no variables were found to be significantly related to treatment completion, but this may be due to the small sample size and due to the fact that the majority who started treatment also completed it.

When looking at the survival of all patients who were eligible for R-CHOP (≤80), it comes to no surprise that the in-patient group had inferior outcomes. The same is true when looking just at the R-CHOP cohort - the in-patient group that started R-CHOP had a lower survival than the outpatient group in which R-CHOP was initiated. Whether one is looking at patients who were eligible to receive R-CHOP, or those who were eligible and actually received R-CHOP, patients in the in-patient setting had a lower overall survival when compared to the outpatient setting. For reasons explain previously (higher IPI, rapidly advancing disease), this was expected.

There was of course a difference in overall survival between those who completed treatment, and those who did not; something seen in both treatment settings. However, when comparing the in-patient and outpatient groups that completed R-CHOP treatment within the expected 15 weeks duration, the survival difference between the two groups became non-significant. Furthermore, when in-patients and outpatients that completed R-CHOP therapy were stratified by IPI status, the survival rates between these two groups became even more similar.

Consequently, while a significant difference in overall survival between in-patients and outpatients exists, this difference becomes less apparent and less significant the more one stratifies these two groups according to disease presentation and treatment completion.

However, the majority of the in-patients did present with poorer risk factors at diagnosis, and only a small number of in-patients will have a low IPI and a favorable outlook, compared with the outpatient group. Despite these similar survival rates, in-patients with a poor IPI were treated much sooner than the outpatient group. It is therefore interesting that the significant delay in the treatment initiation for the outpatient group did not result in inferior outcomes. This will need to be further evaluated in a larger sample of patients, or a longer follow-up of current patients, while using a Cox regression model.

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Table 1: Sample Characteristics

		All Patients			R-CHOP/80 and younger subgroup	
		In-patient (n=46)	Outpatient (n=96)		In-patient (n=28)	Outpatient (n=64)
		N (%)	N (%)		N (%)	N (%)
Age		68.3 (SD=14.2)	65.2 (SD=15.3)		63.2 (SD=12.2)	58.8 (SD=13.0)
	R-CHOP	28 (60.8)	69 (71.9)			
Chemotherapy	Alternate	4 (8.7)	18 (18.8)			
	No chemo	14 (30.4)	9 (9.4)			
Residence	Rural	23 (50)	27 (28.1)		16 (57.1)	21 (32.8)
	Winnipeg	23 (50)	69 (71.9)		12 (42.9)	43 (67.2)
	0	0	9 (9.4)		0	8 (12.5)
	1	3 (6.5)	27 (28.1)		3 (10.7)	21 (32.8)
IPI	2	7 (15.2)	32 (33.3)		5 (17.9)	19 (29.7)
	3	14 (30.4)	19 (19.8)		6 (21.4)	11 (17.2)
	4	19 (41.3)	9 (9.4)		12 (42.9)	5 (7.8)
	5	3 (6.5)	0		2 (7.1)	0
Gender	F	22 (47.8)	50 (52.1)		13 (46.4)	30 (46.9)
	M	24 (52.2)	46 (47.9)		15 (53.6)	34 (53.1)
	I	10 (21.7)	27 (28.1)		4 (14.3)	16 (25)
Stage	II	7 (15.2)	20 (20.8)		6 (21.4)	15 (23.4)
	III	5 (10.9)	25 (26.0)		2 (7.1)	19 (29.7)
	IV	24 (52.2)	24 (25)		16 (57.1)	14 (21.9)
Symptoms	A	17 (37.0)	66 (68.8)		10 (35.7)	45 (70.3)
	B	29 (63.0)	30 (31.2)		18 (64.3)	19 (29.7)

Table 2: Predicting R-CHOP completion (80 and younger)

		Treatment Completion		
		No (n=16)	Yes (n=76)	p-value
		N (%)	N (%)	
Age		62.3 (SD=12.6)	59.70 (SD=13.0)	0.4744
Treatment Setting	In-patient	7 (43.8)	21 (27.6)	0.2028
	Outpatient	9 (56.2)	55 (72.4)	
Residence	Rural	6 (37.5)	31 (40.8)	0.8073
	Winnipeg	10 (62.5)	45 (59.2)	
	0	2 (12.5)	6 (7.9)	
	1	3 (18.8)	21 (27.6)	
IPI	2	4 (25.0)	20 (26.3)	0.677 (3+ vs. 0-2)
	3	4 (25.0)	13 (17.1)	
	4	2 (12.5)	15 (19.7)	
	5	1 (6.2)	1 (1.3)	
Gender	F	7 (43.8)	36 (47.4)	0.792
	M	9 (56.2)	40 (52.6)	

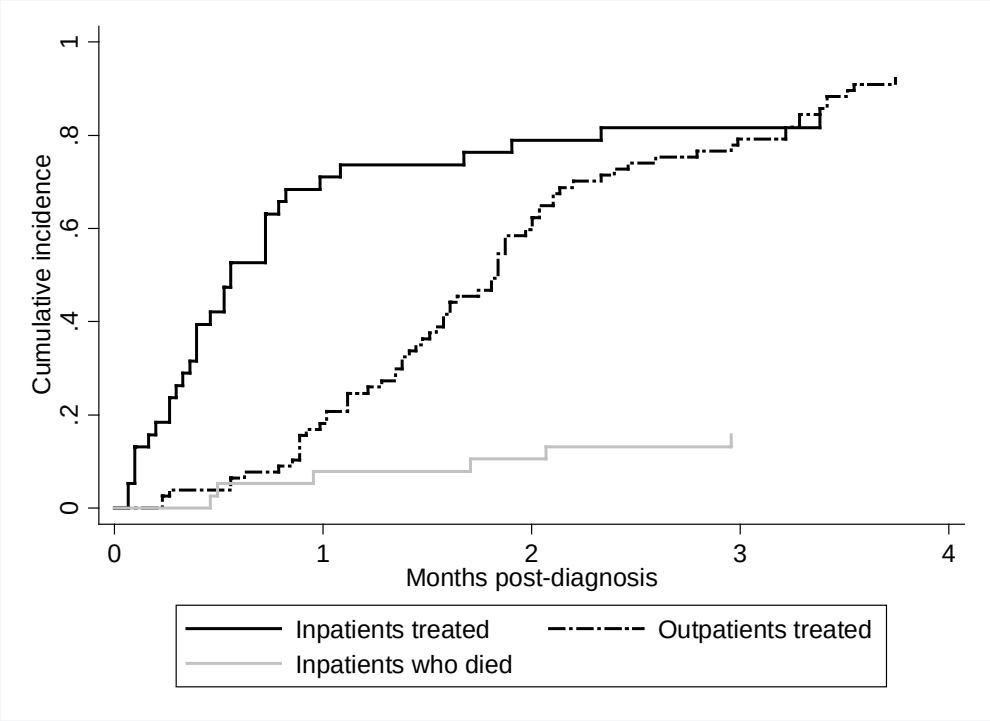

Figure 1: Cumulative incidence of treatment and death by setting for patients who are eligible to receive R-CHOP

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Figure 2: Overall Survival post-diagnosis for those eligible to receive R-CHOP by treatment setting

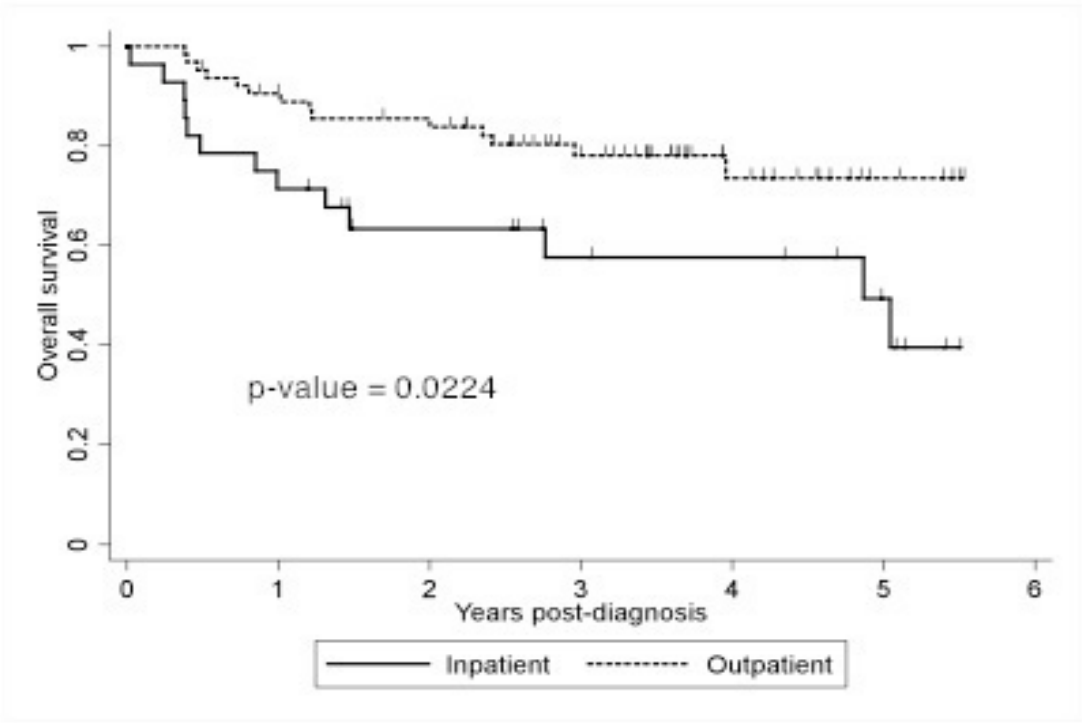

Figure 3: Overall survival post-diagnosis for R-CHOP eligible and treated patients by treatment setting

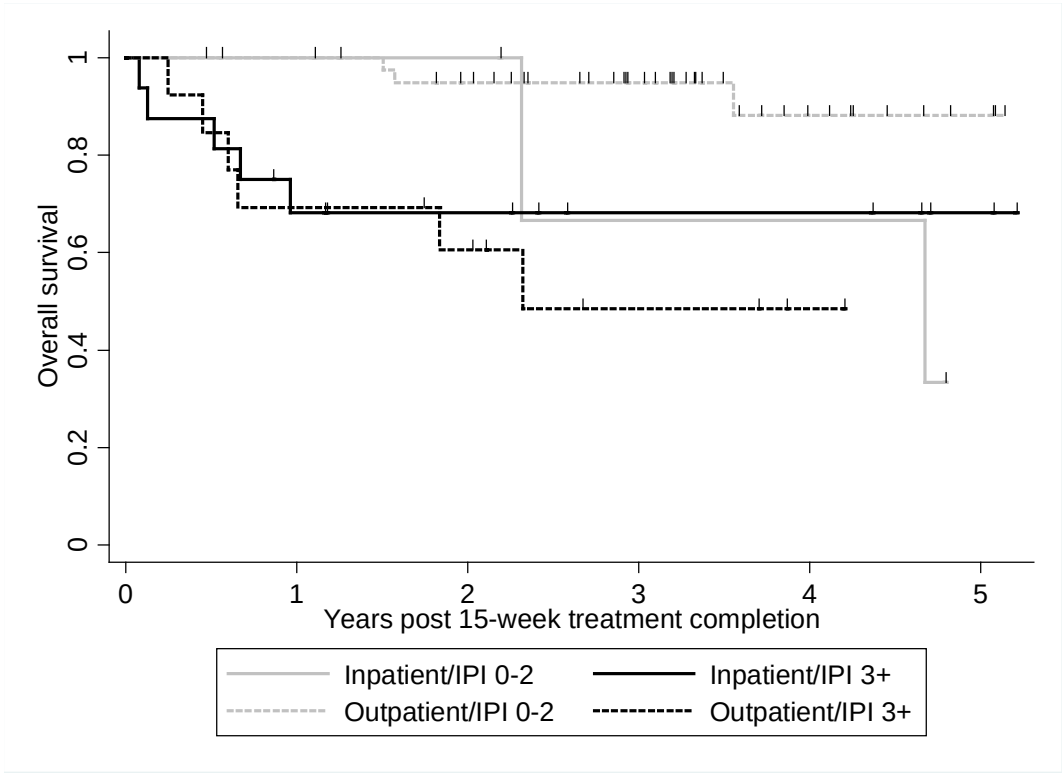

Figure 4: Overall survival after R-CHOP treatment completion by setting and IPI status