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Analysis of immunometabolic and nutritional scoring systems and the body-mass-index as prognostic markers for treatment outcomes in patients undergoing allogeneic hematopoietic stem cell transplantation

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Prof. Dr. med. Sebastian Theurich
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Die dieser Arbeit zugrundeliegenden Daten wurden durch meine Arbeit in der Abteilung für Hämatologie und Onkologie in der Klinik I für Innere Medizin der Universität zu Köln und der Universitätsklinik Bonn ermittelt.

Alleinig bei den Nachsorgeuntersuchungen der Patienten wurde ich von der medizinischen Dokumentationsassistentin Silke Leitzke unterstützt.

Die statistische Auswertung habe ich in Abstimmung mit und Anleitung durch meinen betreuenden Doktorvater Herrn Prof. Dr. med. Sebastian Theurich durchgeführt.

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“He who has a why to live can bear almost any how”

-Friedrich Nietzsche

In diesem Sinne möchte ich danke sagen: meiner Familie und meinen Freunden -für die immerwährende Unterstützung

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Meiner lieben Familie - in toto

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1 Summary

Introduction: This study examines the potential impact of metaflammation on the outcomes of allogeneic stem cell transplantation by using the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) to assess the risk of therapy-associated morbidity and mortality. Obesity is considered a significant risk factor, quantified according to the Body Mass Index (BMI) introduced by the World Health Organization (WHO). Chronic systemic inflammation is considered a molecular biological pathomechanism associated with obesity; interactions between hypertrophied adipose tissue and the immune system are summarized with the term "metaflammation." This study was conducted under the hypothesis that recipient-related metaflammation could influence the outcome of allogeneic stem cell transplantation.

Project description: Clinical data and routinely acquired laboratory data were analyzed from patients undergoing allogeneic stem cell transplantation at the department for internal medicine (“Klinik I für Innere Medizin”) at University Hospital Cologne between 2012 and 2017. In addition to BMI, metabolic and immunological laboratory parameters were collected. The primary endpoints of the analyses were overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), and the incidence as well as severity of acute graft-versus-host-disease (aGvHD/GvHD-I).

Materials and methods: Laboratory- and transplantation-specific data as well as general patient data were collected before beginning of conditioning therapy and up to day 100 post-transplantation. The analysis of the total cohort and a homogeneous subgroup was performed based on gender characteristics and BMI. The subgroup was characterized by the following features: conditioning therapy performed with reduced intensity, matched-related donor/matched unrelated donor and 10/10 HLA and peripheral stem cell source.

Results: A total of 461 patient cases were included in the analyses. A subgroup consisting of 251 patients was formed. In the gender-specific analysis, the group of overweight male patients (BMI 25-29.9) had the best survival rate at 62% after 69 months (p-value 0.0082** log-rank test). The female total cohort showed a survival advantage in the group with BMI ≥25 and also in BMI >30. Patients with BMI >30 had the highest incidence of aGvHD and there was an association with high non-relapse-mortality (NRM). Evaluations of nutritional status based on systemic inflammatory response using the Glasgow Prognostic Score showed the following

results in the total cohort immediately after engrafting on day 30: hypoalbuminemia corresponding with malnutrition and simultaneous systemic inflammation reaction showed the lowest survival rate at 15% after 57 months (GPS 2) compared to 48% in GPS 0 and 44% in GPS 1, each measured after 60 months (p-value <0.0001*** log-rank test); Patients with GPS 2 also showed the highest NRM with 71% deceased patients after 57 months compared to an NRM rate of 23% in GPS 0 and 35% in GPS 1 after 60 months.

Conclusion: Gender-specific differences were observed in overall survival: a BMI >25 and also >30 appeared to have a survival advantage for female patients. In contrast, male transplant recipients only showed a survival advantage in the BMI group >25-30. A BMI >30 had a negative influence on survival in the male cohort. Nutritional status also had a major impact in our analyses, as overweight and malnutrition were investigated independently. However, overweight can appear with malnutrition and also with chronic inflammatory reaction: Malnutrition combined with high NLR and inflammation seems to present a significant negative prognostic factor. Thus, gender-specific investigations and nutritional status along with meta-inflammatory components influence the outcomes of alloHSCT. This study is limited by retrospectively collected data and a small cohort.

Besides already established risk assessment scores, it may be possible to develop additional valid scores assessing the nutritional status of the transplant patient and including conditions such as sarcopenia or malnutrition. In the context of allogeneic stem cell transplantation, further prospective cohort studies with larger patient numbers are necessary to validate the scores developed and analyzed in this thesis. The clinical application of scores related to other oncological diseases is also conceivable and should be investigated interdisciplinary in oncological studies.

1.1 Zusammenfassung

Einleitung: Diese Arbeit untersucht die mögliche Auswirkung von Metaflammation auf die Ergebnisse einer allogenen Blutstammzelltransplantation, indem sie den Hematopoietic Cell Transplantation-Comorbidity Index (HTC-CI) verwendet, um das Risiko für therapieassoziierte Morbidität und Mortalität abzuschätzen. Adipositas wird als bedeutsamer Risikofaktor angesehen, welcher nach dem Body-Mass-Index (BMI) der World Health Organization (WHO) quantifiziert wird. Ein molekularbiologischer Pathomechanismus in Zusammenhang mit Adipositas ist die chronische systemische Inflammation; Interaktionen aus hypertrophiertem Fettgewebe und Immunsystem werden unter dem Begriff „Metaflammation" zusammengefasst. Unter der Hypothese, dass eine empfängerbedingte Metaflammation die Ergebnisse einer allogenen Blutstammzelltransplantation beeinflussen könnte, wurde diese Arbeit verfasst.

Projektbeschreibung: Klinische Daten sowie Routinelabordaten wurden von jenen Patienten analysiert, die sich 2012 - 2017 einer allogenen Blutstammzelltransplantation an der Klinik I für Innere Medizin, Universitätsklinik Köln unterzogen haben. Neben dem BMI wurden metabolische und immunologische Laborparameter erhoben. Als primäre Endpunkte der Analysen wurden das Gesamtüberleben (OS), das progressionfreie Überleben (PFS), die Non-Relapse-Mortality (NRM) und die Inzidenz sowie Schwere der akuten Graft-versus-Host-Reaktion (aGvHD/GvHD-I) gewählt.

Arbeitsprogramm/Material und Methoden: Erfasst wurden allgemeine, laborchemische und transplantationsspezifische Daten vor Konditionierungstherapie und bis Tag 100 nach Transplantation. Die Auswertung der Gesamtkohorte und einer homogenen Subgruppe erfolgte nach Geschlechtsmerkmalen und BMI. Charakterisiert wurde die Subgruppe durch folgende Merkmale: mit reduzierter Intensität durchgeführte Konditionierung, matched-related donor/matched-unrelated donor und 10/10 HLA sowie peripherer Blutstammzellquelle.

Ergebnisse: Es wurden insgesamt 461 Patienten in die Analysen einbezogen. Es wurde eine Subgruppe mit 251 Patienten gebildet. Bei der geschlechtsspezifischen Auswertung hatte die Gruppe der übergewichtigen, männlichen Patienten (BMI 25-29,9) die beste Überlebensrate mit 62% nach 69 Monaten (p- Wert 0.0082** Log-rank Test). Die weibliche Gesamtkohorte

zeigte einen Überlebensvorteil in der BMI-Gruppe ≥25 und auch in der Gruppe mit BMI >30. Patientinnen mit BMI >30 hatten die höchste aGvHD Inzidenz. Gleichzeitig zeigte sich eine Assoziation mit hoher Non-Relapse Mortality (NRM) bei Patientinnen mit BMI >30. Auswertungen zum Ernährungszustand auf Grundlage systemischer Entzündungsreaktion anhand des Glasgow-Prognostic-Scores zeigten in der Gesamtkohorte direkt nach Engrafting an Tag 30: Hypalbuminämie entsprechend Mangelernährung und eine gleichzeitig systemische Inflammationsreaktion zeigten das geringste Überleben mit 15% nach 57 Monaten (GPS 2) im Vergleich zu 48% in GPS 0 und 44% in GPS 1, jeweils nach 60 Monaten gemessen (p- Wert <0.0001*** Log-rank Test); Patienten mit GPS 2 zeigten auch die höchste NRM mit 71% verstorbenen Patienten nach 57 Monaten, im Vergleich dazu war die NRM-Rate in GPS 0 nach 60 Monaten 23% und in GPS 1 35%.

Schlussfolgerung und Ausblick: Geschlechtsspezifisch zeigten sich Unterschiede im Gesamtüberleben: ein BMI >25 und auch >30, schien für Patientinnen ein Überlebensvorteil zu sein. Diametral dazu standen männliche Transplantierte, die nur in der BMI-Gruppe >25-30 einen Überlebensvorteil zeigten. Ein BMI >30 hatte ein negativ prognostisches Überleben in der männlichen Kohorte. Der Ernährungsstatus spielte ebenfalls eine Rolle in unseren Auswertungen: Übergewicht und „Fehlernährung“ sind unabhängig voneinander untersucht worden. Übergewicht kann jedoch mit Mangelernährung einhergehen und auch mit chronischer Inflammationsreaktion: Eine Mangelernährung in Kombination mit hoher NLR und Inflammation bilden zusammen einen bedeutsamen negativ prognostischen Faktor. Sowohl geschlechtsspezifische Untersuchungen als auch der Ernährungszustand und metinflammatorische Komponenten beeinflussen Ergebnisse der alloHSCT. Diese Arbeit ist durch retrospektiv erhobene Daten und einer kleinen Kohorte limitiert.

Möglicherweise lassen sich neben bereits etablierter „risk assessment scores“ weitere valide Scores entwickeln, die individuell auf den Ernährungsstatus des Transplantationspatienten zugeschnitten sind und Merkmale wie Sarkopenie oder Malnutrition inkludieren. Für das Setting der allogenen Stammzelltransplantation sind weiterführende prospektive Kohortenstudien mit höheren Patientenzahlen notwendig, um die in dieser Doktorarbeit analysierten Scores in Ihrer Aussagekräftigkeit zu validieren. Eine Anwendung der Scores bezogen auf andere onkologische Erkrankungen ist ebenso denkbar und sollte interdisziplinär bei onkologischen Studien untersucht werden.

Abbreviations

aGvHD	Acute graft-versus-host-disease
aGvHD-I	Incidence of aGvHD
alloHSCT	Allogeneic hematopoietic stem cell transplantation
BIA	Bioelectric impedance analysis
BMI	Body mass index
CD	Cluster of differentiation
cGvHD	Chronic graft-versus-host-disease
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNG	C-reactive protein-protein ratio
CRP	C- reactive protein
d+0	Day of transplantation
d+30	30 days post transplantation
d+100	100 days post transplantation
GPS	Glasgow-prognostic score
HCT-CI	Hematopoietic cell transplantation-specific comorbidity index
HL	Hodgkin lymphoma
HLA	Human leucocyte antigen
HSCT	haematopoietic stem cell transplantation
IL-R2+	Interleukin-receptor 2 positive
IMS	Immuno-Metabolic Score
kgBW	kilogram body weight
MAC	Myeloablative conditioning

mGPS	modified Glasgow-Prognostic Score
MRD	Matched related donor
MUD	Matched unrelated donor
NHL	Non-Hodgkin lymphoma
NLR	Neutrophil-to- lymphocyte ratio
NRM	Non-relapse mortality
OS	Overall survival
PCM	Plasma cell myeloma
PCR	Protein-CRP-ratio
Peri Tx	peri transplant period
PFS	Progression-free survival
Prior Tx	Prior transplantation (= prior conditioning regime)
RI	Relapse incidence
RIC	Reduced intensity conditioning
Tx	Transplantation
URD	Unrelated donor
WTHR	Waist-to-hip-ratio
WHO	World Health Organization

Description

CD3+	Part of the T-cell receptor complex and represents a marker for all T cells
CD4+	Glycoprotein and a marker of T- helper cells
CD8+	Co-receptor of the T-cell receptor and a marker of cytotoxic T- cells
CD16+	Fc receptor and expressed by natural killer cells, monocytes and some T cell subpopulations
CD56+	Neural cell adhesion molecule 1 (NCAM1) that is expressed on natural killer cells and neurons.
CD19+	B-Lymphocyte Surface Antigen
CD34+	Receptor, positive to the transmembrane phosphoglycoprotein protein encoded by the CD34 gene, characteristically for stem cells
HLA- DR	MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6

2 Introduction

Nutritional status plays a vital role in determining the Non-Relapse-Mortality of patients undergoing allogeneic hematopoietic stem cell transplantation. In contrast to underweight, the role of overweight and obesity for alloHSCT outcomes is not well understood. In this thesis, the body mass index is analyzed as an indicator of metabolic risk.

Using data from alloHSCT patients, this retrospective analysis considers various factors such as body composition, sex differences, nutrition, and immunometabolic reactions. Peritransplant outcomes are evaluated using the Glasgow-prognostic score, CNG, and Neutrophil-to-lymphocyte ratio.

2.1 Overweight and obesity as medical risk factors

Overweight and obesity pose significant health risks especially in western or industrial countries caused predominantly by hypercaloric and energy-dense nutrition habits and a sedentary lifestyle (Obesity: preventing and managing the global epidemic. Report of a WHO consultation 2000a). According to the WHO, there are over 1 billion overweight adults worldwide with the incidence of these conditions steadily increasing (Zheng et al. 2011; Abelson et al. 2004). Pathologic adipose tissue accumulation has been associated with cardiovascular and endocrinological conditions such as coronary heart disease, arterial hypertension and type II diabetes. However, in recent years numerous studies have also shown that overweight and obesity are significant risk factors for cancer and can influence the outcome of stem cell transplantation and chemotherapies. The interaction of obesity, altered pharmacokinetics and the significant role of comorbidities make it challenging to determine the correct dosage of cancer therapies (Nikolousis et al. 2010; Vogl et al. 2011).

The growing incidence of obesity and the subsequent increase in overweight patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) highlight the need for greater attention to the assessment and implementation of alloHSCT both now and in the future. Overweight and obesity are defined using the body-mass-index (BMI). The BMI is calculated as the result of dividing body weight by the square of height, measured in kilograms

per square meter (kg/m²). (Obesity: preventing and managing the global epidemic. Report of a WHO consultation 2000a).

Category	BMI [kg/m²]	Risk for secondary diseases
Underweight	<18.5	low
Normalweight	18.5-24.9	normal
Overweight	25-29-9	slightly increased
Obesity °I	30-34.9	increased
Obesity °II	35-39-9	strongly increased
Obesity °III	≥40	extremely increased

Table 1: BMI WHO classification

2.2 Definition of overweight and indicators (medical measurement tools)

The Body Mass Index (BMI) is an instrument for measuring overweight and obesity. However, it cannot provide information on fat distribution, muscle mass or body constitution. Obesity is measured and quantified through the BMI. The weight categories listed in Table 1 have been correlated to Caucasian body composition and silhouette. Apart from differing size and body fat composition between men and women, there are also ethnical distinctions which should be considered. For example, a varying average body size and shape can be observed in Asia compared to Europe. Studies indicate that the BMI weight categories used on Caucasians should be adjusted downwards when applied to Asians. In contrast, with African countries and even some Nordic countries in Europe, an upward shift to the weight categories is needed. The issue that arises from differences in ethnicity is the potential for the standard BMI to underestimate or overestimate the health status of a diverse group of individuals. (Gomersall et al. 2014; Rissanen et al. 1991; Wen et al. 2009)
In order to assess the health risk more accurately, alternative indicators considering gender, age, co-morbidity and fat distribution have been introduced. These are described further in the following paragraphs.

The distribution pattern of body fat plays a key role in assessing metabolic and cardiovascular health risks. A larger amount of visceral fat is associated with a greater cardiovascular risk and its underlying conditions. (Despres et al. 2001)

The waist circumference is an indicator of visceral fat deposition (Lean et al. 1995). A waist circumference of ≥ 88 cm for women and ≥ 102 cm for men indicates abdominal obesity (Obesity: preventing and managing the global epidemic. Report of a WHO consultation 2000b; Janssen et al. 2002a; Janssen et al. 2002b). Individual risk factors, comorbidities and the body shape help completing a comprehensive health risk assessment of a patient (Obesity: preventing and managing the global epidemic. Report of a WHO consultation 2000b; Weiss et al. 2013 recommend the use of waist circumference as opposed to BMI in older patients, since body size and muscle mass decrease with higher age. (Perissinotto et al. 2002).

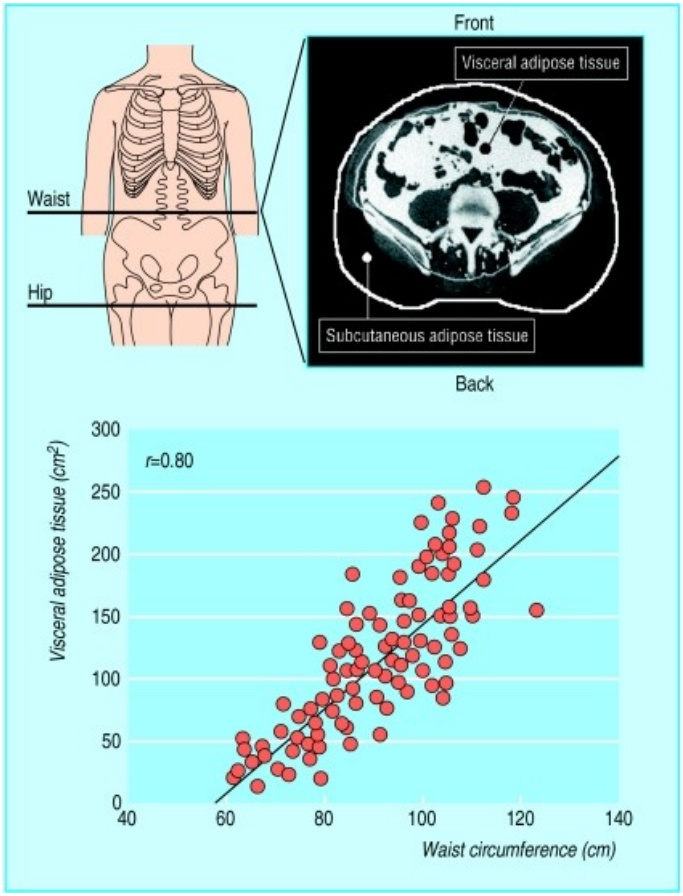


Figure 1: Relation of waist circumference and visceral adipose tissue (Despres et al. 2001)

The waist-to-hip ratio (WTHR) is another indicator derived from the waist circumference. It is calculated by dividing the circumference of the waist by the circumference of the hips. (Despres et al. 2001).

A higher WTHR, in accordance with a higher waist circumference, indicates that a greater amount of fat is stored around the waist (see Figure 1). Visceral fat tissue is metabolically

active and poses a health risk through various pathomechanism associated with metabolic syndrome (Despres et al. 2001).

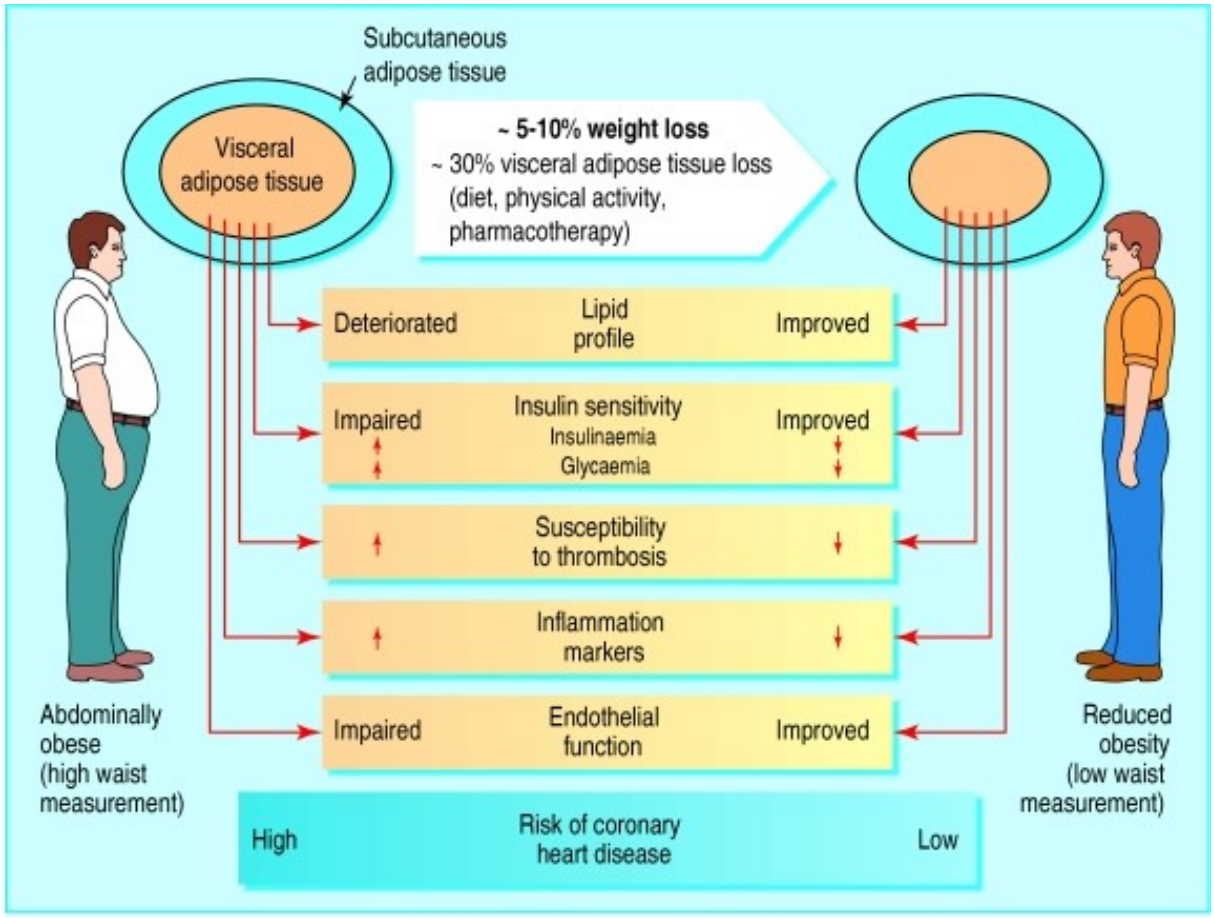


Figure 2: Metabolic activation in abdominally obese patients (Despres et al. 2001)

Ongoing radiological studies are working towards developing imaging software that can accurately calculate the volume and distribution of fat in the human body. One such technique involves using dual-energy X-ray absorptiometry (DXA) scans to detect both fat and lean body mass. Thus, this type of imaging can be used to assess a patient's overall muscle or fat mass. Furthermore, with DXA scans it is also possible to distinguish between central and peripheral fat deposits by using a specific density setting for fat tissue. (Kullberg et al. 2009)

Magnetic resonance imaging (MRI) or computer tomography (CT) are alternative imaging methods, which can also be applied to differentiate and measure visceral and subcutaneous fat. Due to differences in the technical principle, there is no radiation exposure with MRI scans and therefore can potentially be used more often without risk of a health hazard. As a result thereof, MRI scans may be especially beneficial compared to CT scans in cancer and

immunedeficiency patients, who are already exposed to potent radiation and chemotherapy cycles due to their initial diagnosis. (Kullberg et al. 2009; Müller et al. 2011)

2.3 The role of obesity in the pathogenesis of haemato-oncological disorders - pathomechanism and correlations

Several studies have shown molecular, genetic and immunological factors regarding the correlation between haemato-oncological disorders and weight-associated comorbidities. In particular, obese patients have an increased risk for chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), Non-Hodgkin's and Hodgkin's lymphoma as well as plasma cell myeloma (PCM) (Calle et al. 2003; Chiu et al. 2006; Engeland et al. 2007; Merchav 1998; Renehan et al. 2008; Birmann et al. 2007; Friedman et al. 1994). Yet, there is no definite conclusion whether obesity adversely affects non relapse mortality (NRM), Tumor-related mortality and relapse incidence (RI) (Fleming et al. 1997a; Weiss et al. 2013a).

In this regard, the insulin hormone receptor was found on human ALL, AML and CML (Chen et al. 1983; Saiya-Cork et al. 2011). On CLL cells, researchers have found very high insulin receptor expression, which leads to the conclusion that CLL is affected by insulin-dependent regulatory processes. IGF-1 receptors have been found on myeloid and lymphoid leukaemia cells, which is indicative of an increased expression of tumor specific and inflammation pathways: the PI3K/Akt-mTOR pathway (Shimon et al. 1995; Saiya-Cork et al. 2011; Tamburini et al. 2008). Also, leptin receptors have been found to be expressed of hematopoietic progenitor cells as well as on ALL; AML, APL and CML cells (Ozturk et al. 2012; Chapuis et al. 2010; Nakao et al. 1998; Konopleva et al. 1999; Bruserud et al. 2002). Nakao et al (1998) found out that CML cells during CML blast crisis express a higher level of leptin receptors.

Recent studies have shown that immunologic or metabolic receptors are expressed on the surface on cancer cells. This leads to the conclusion that cancer cells are strongly influenced by immunological or inflammatory processes. There has also been evidence suggesting a correlation between cancer development and growth and metabolic processes in an obese body. Weiss et all (2013) also assumes that there are potential mechanisms by which adipose tissue may stimulate leukemic growth and may contribute to the increased risk for solid

tumors as well (Weiss et al. 2013b). One possible target for future immune-chemotherapies may be lipid metabolic processes such as PI3K-AKT-mTOR. Monoclonal antibodies could inhibit this receptor or neutralize its activity altogether (Martelli et al. 2003; Yu et al. 2005; Wong et al. 2010).

2.4 Effects of obesity on drug pharmacokinetics

The pharmacokinetics of drugs can be affected by obesity, which is particularly relevant in oncology, where high-dose chemotherapy is administered to treat solid and haematological tumours. Lipophilic drugs, commonly used in chemotherapy, have been shown to have their distribution and storage altered in adipose tissue. (Blouin et al. 1987)

Overweight subjects are more commonly affected by internal co-morbidities such as diabetes mellitus and cardiovascular diseases. These can complicate cancer therapy due to concerns about putting excessive strain on affected organ systems. (Tisdale 2009)

The production of inflammatory mediators such as cytokines might be the origin of cancer-associated cachexia. Therefore, overweight patients can also be affected by tumour cachexia. Yet, there are some studies suggesting adaptations of therapy in obese cancer patients. Currently, decisions regarding drug therapy are usually based on the clinical situation. It remains a scientific question whether the implementation of more standardized and multivariate evaluation methods, with the exclusion of certain patient groups, holds promise for improving these processes. (Weiss et al. 2013a)

2.5 Overweight as a risk factor for metabolic stress

Overweight adults are exposed to different risk factors than normal weighted adults, including an elevated risk of cancer and cardiovascular disease, as well as metabolic disorders resulting from increased fat metabolism (Nakao et al. 2014). There is currently not sufficient evidence for obesity to be considered a proven risk factor for a negative outcome in hematopoietic stem cell transplantation (HSCT). (Nikolousis et al. 2010)

2.5.1 Sarcopenia and sarcopenic obesity

There is a correlation between sarcopenia and obesity leading to the term of “sarcopenic obesity”. In recent years, an increasing prevalence in sarcopenic obesity has been reported worldwide. Evidence suggests an aging population as well as changes in lifestyle in recent years to be contributing factors. Sarcopenia is defined as “the result of a reduction in motor unit number together with atrophy of muscle fibers”. There is yet no consensus on the definition of sarcopenic obesity. (Thomas 2007)

Low muscle mass, low muscle strength as well as high body fat are considered as relevant features (Molino et al. 2016). The pathogenesis of sarcopenic obesity is multifactorial including factors such as physical inactivity, insulin resistance, discharge of adipokines and myokines, inflammation as well as oxidative stress. This results in a decline in muscle mass (quantitatively and qualitatively) whereas the fat mass increases (Polyzos and Margioris 2018; Wannamethee and Atkins 2015). As aging is often associated with inevitable weight loss, sarcopenic obesity can often remain masked (Benton et al. 2011).

2.5.2 Obesity-associated metabolic processes

Obesity is defined as a chronic disease, which results from an imbalance of energy intake and utilization (Weiss et al. 2013d). This imbalance is influenced by factors such as physical activity, psychosocial factors, sleep and environment (Storfer-Isser et al. 2012). These factors lead to an expansion of number and size of adipocytes (Tchoukalova et al. 2008; Mundi et al. 2010).

Adipose tissue is an endocrine organ. It does not only store inactive energy, but also activates intensive metabolic processes. Specific hormones called adipokines such as leptin and adiponectin are synthesized in fatty tissue. They circulate through the system and influence systemic hormone concentrations. Regulated hormones are insulin, insulin-like growth factor and sex steroids, all of which have an influence on cell growth. Consequently, these hormones and their key messengers can also regulate cancer growth. (Calle und Kaaks 2004)

In addition to the production of adipokines, fatty tissue also contains hematopoietic stem cells. Experimental studies have found out that these stem cells derived from adipose tissue have the ability to save lethally irradiated rodents – this is called the “sanctuary site effect”. (Han et al. 2010; Cousin et al. 2003; Behan et al. 2009)

Furthermore, adipocytes also regulate chronic inflammation: Resident macrophages and adipokines can trigger a local inflammatory response. As a result, systemic cytokines such as TNF-alpha and interleukin-6 are released. T cells are then regulated through the resulting systemic inflammation cascade. (Horng and Hotamisligil 2011; Yang et al. 2010; Feuerer et al. 2009). Adipose tissue has impacts on hormone metabolism and systemic inflammation (Villaret et al. 2010).

2.5.3 Key mechanisms in adipose tissue leading to carcinogenesis

Up to 50% of all cancer subtypes (leukaemia included) are directly related to obesity, which in turn is associated with metabolic disorders also affecting the immune system (Calle and Kaaks 2004; Pergola and Silvestris 2013). Obese patients produce increased levels of hormones (oestrogens, adipokines, insulin), that potentiate the risk of developing cancer. The carcinogenic effects of these molecules include promoting cell survival, proliferation and growth in the tumour cell. Furthermore, processes such as the dysregulation of metabolic signalling are influenced (e.g. mTOR and AMPK) which can foster tumour growth directly (Font-Burgada et al. 2016).

There is a bidirectional interaction between immune cells and metabolism, called immunometabolism (Ray et al. 2016). Hotamisligil discovered elevated activity of tumour necrosis factor in adipose tissue. Ferrante and Chen's group detected macrophage infiltrations in the adipose tissue of obese mice, which leads to inflammation in this tissue (Hotamisligil et al. 1993; Weisberg et al. 2003b; Xu et al. 2003). In normal-weight individuals, interleukins like IL-4, IL-10 and IL-13 maintain insulin-sensitivity and anti-inflammatory metabolism. Obesity causes a release of pro-inflammatory fatty acids and simultaneously induces lipolysis. Furthermore, the increase in TNF-alpha causes monocytes to migrate from the blood and infiltrate the adipose tissue, where they convert into the pro-inflammatory M1 types. At the same time, anti-inflammatory cell types such as eosinophils and T-regulatory cells are suppressed, while CD4+ Th1 and CD8+ effector cell amounts increase (Shi et al. 2006; Suganami et al. 2005; Nguyen et al. 2005; Lumeng et al. 2007).

This immunologic effect in obesity also influences cancer cells: Adipose tissue causes chronic low-grade inflammation (Kohlgruber et al. 2016). Immune cells change from a tolerogenic anti-inflammatory phenotype to a pro-inflammatory response. Pro-inflammatory

macrophages from adipose tissue expand (Weisberg et al. 2003a; Zheng et al. 2016). Studies have found out that chronic low-grade inflammation can in turn stimulate carcinogenesis by activating transcription factors such as NFkB, JNK and STAT3 (Font-Burgada et al. 2016).

2.6 Allogeneic haematopoietic stem cell transplantation (alloHSCT)

Allogeneic stem cell transplantation is an immunomodulatory therapy, which has been used in haematology for more than 30 years to treat conditions such as severe aplastic anaemia and immunodeficiency (Kai and Hara 2003). However, due to its complexity there is a high risk of therapy-related morbidity and mortality (Kröger 2016; Majhail et al. 2015).

Obesity is often problematic in patients undergoing alloHSCT. Reports on this patient group show heterogeneous definitions of weight (see also chapter 2.7), underlying comorbidities, different graft sources and chemotherapies. It appears that obese patients have a higher non-relapse mortality (NRM) and inferior survival when undergoing alloHSCT. An altered pharmacokinetic resulting from obesity has been identified as a contributing factor for unexpected events during the transplantation course (Weiss et al. 2013c). Statistically, obesity is associated with an increased overall and cancer-specific mortality (Calle et al. 1999; Calle et al. 2003).

2.7 Comparison of studies using different obesity and BMI definitions

Several studies suggest an inferior outcome and increased NRM in obese patients undergoing alloHSCT. In these studies, variable instruments have been used to define obesity. (Fleming et al. 1997a; Hansen et al. 1998; Fuji et al. 2014; Fuji et al. 2009; Navarro 2013; Navarro et al. 2010; Nikolousis et al. 2010; Thyagarajan et al. 2010)

Two studies (Fuji et al. 2009; Fuji et al. 2014) analysed the impact of pretransplant body mass index (BMI) on the clinical outcome. They performed a “retrospective study with registry data including a total of 12 050 patients (age ≥18 years) who received allogeneic hematopoietic SCT (HSCT) between 2000 and 2010” (Fuji et al. 2014).

Fuji et al. defined BMI as follows: “BMI<18.5 kg/m², Underweight, n=1791; 18.5≤BMI<25, Normal, n=8444; 25≤BMI<30, Overweight, n=1591; BMI≥30, Obese, n=224. The median age was 45 years (range, 18-77).” Data was analysed with multivariate analyses, which showed a significantly higher risk of relapse in the underweight group. The relapse incidence was lower in the overweight and obese groups compared with the normal group (hazard ratio (HR), 1.16, 0.86, and 0.74, respectively). The risk of graft-versus-host-disease (GvHD) was significantly higher in the overweight subjects in comparison to the normal weight. The risk of non-relapse mortality (NRM) was significantly higher in the overweight and obese group compared with the normal group (HR 1.19 and HR 1.43, respectively). The probability of overall survival was lower in the underweight group compared with the normal group (HR 1.10, P=0.018). Pretransplant BMI affected the risk of relapse and NRM after allogeneic HSCT. Consequently, underweight was a risk factor for poor overall survival because of an increased risk of relapse. Obesity was a risk factor for NRM. Fuji suggests that obesity might affect the transplant course regarding a higher rate of complications rather than influencing the pharmacokinetics.

One immunological complication after alloHSCT is the acute graft-versus-host-disease (aGvHD, acute is defined as “within 100 days after transplantation”) (Weisdorf 2007). The pathogenesis of GvHD includes the toxicity of conditioning regimen that expose neoantigens or enhance cytokine releases and thus initiate an immunologic storm (Przepiorka et al. 1995). Donor T-cells facilitate alloantigen recognition. After activation, they first migrate into lymphoid organs, from which they later expand into peripheral tissue. In the following, a cytokine storm is activated and aGvHD manifests due to cytolysis and apoptosis. GvHD affects the skin, eyes, gut and liver. In patients with related donors (e.g. a sibling), acute GvHD occurs in 30-50% of alloHSCT. Due to a higher histoincompatibility, GvHD arises more commonly in patients with Unrelated Donors (URD). This patient group partly shows an enhanced antitumor effect, while the risk of developing a chronic GvHD as well as secondary infections is increased (Przepiorka et al. 1995).

2.8 Objectives and Hypotheses

This thesis investigates in a retrospective analysis the role of immunometabolic and nutritional scoring systems as well as the body-mass-index as prognostic markers for treatment outcome in patients undergoing allogeneic hematopoietic stem cell transplantation.

For this purpose, the following objectives and hypotheses were developed:

- How does BMI influence the OS, NRM, aGVHD-I and PFS after alloHSCT? How is the survival in groups with malnutrition (BMI <18.5 and BMI ≥30)?
- Does overweight have a positive effect on survival and aGvHD incidence?
- Does obesity have a negative effect on survival and aGvHD risk?
- How does BMI-independent variables like sex, conditioning scheme and inflammation influence survival?
- Which role does the “metaflammation” and chronic low-grade-inflammation play in development of an aGvHD?
- Can the stated scores (known from being assessment scores prior Tx) also be used to better accompany transplant patients during follow-up on day 30 and day 100? Can an assessment score prior Tx also be used for the follow up (day 30 and day 100)?
- Does the BMI correlate with chronic low inflammation and malnutrition? Is there a univariate significance?
- Is a body mass index ≥30 kg/m² an independent predictor of inferior outcome?

3 Materials and Methods

3.1 Patient cohort and data

Data was collected and analysed retrospectively from 461 patients who underwent allogeneic hematopoietic stem cell transplantation at the Cologne Transplantation Centre from 03 January 2012 to 01 August 2017.The endpoint was 10 November 2017 as day 100 post Transplantation.

Selection was based on the following inclusion criteria:

- Timeline: January 2012 to November 2017
- Patients with age ≥ 18 years
- Female and male recipients
- patients with former autologous HSCT were included as well
- NO preselection of haematological and/or oncological disease.
- The diagnoses were divided into the following categories: Myeloid neoplasia, lymphatic neoplasia, Non-Hodgkin lymphomas, multiple myeloma, myelofibrosis and hemoglobinopathies/aplastic anaemia
- BMI measured prior Conditioning: The BMI was calculated according to the following formula: BMI= weight (kg)/size (m^2) (WHO)
- There were no other indications for patient exclusion such as age, comorbidity, origin, autologous transplantation or diagnosis.

The following exclusion criteria were used:

- Previous allogeneic HSCT
- Underweight (BMI <18)
- No valid BMI measurements prior Conditioning

Further inclusion and exclusion criteria were applied to analyse a uniform patient cohort (n=251):

- Reduced- Intensity conditioning
- BMI groups: NW, OW, OB and BMI prior Conditioning
- Stem cell source: peripheral blood (CD34+)
- MRD and MUD
- 10/10 matched HLA
- Male and female recipients

Data sets from the years 2012 to 2017 were retrospectively analysed. The measurement of the BMI was a prerequisite for inclusion. Before 2012, it was not common to measure the BMI as a standard procedure. Our research spanned until 2005, but due to resulting insufficient and inconsistent documentation of weight and height, there are several gaps in the data during the earlier years.

For data collection, a data base was provided by the documentation assistant Silke Leitzke with the software Microsoft Access©. In order to register and evaluate all variables and parameters a table was created using the software Microsoft Excel©. Patient data was collected from the medical information systems ORBIS and its digital archive, the Mega Manager, Cato as well as the patient file maker of the outpatient transplant department of the University Hospital of Cologne. Data were entered separately for each patient in the Access database. The tables were then exported to an Excel file.

The database for patient follow-up up to day d+100 after transplantation was provided by Silke Leitzke as well. The above-mentioned collection and documentation software of the University Hospital of Cologne were also used for this purpose. Patients who were in peripheral outpatient or inpatient care were contacted personally or via their attending general practitioners or registered haematological oncologists respectively.

DETAILED CHART OF EXAMINED PARAMETERS (prior Conditioning, on d+30 and d+100: Total Cohort of n=461 Cases- Period of Data Collection: 1.1.2012-10.11.2017 PART 1				
Demographic Data			***Transplantation Setting and Conditioning Regime***	
General Information	**Diagnosis (haematological and/or oncological)**	**Body-Mass Index (BMI according to WHO definition) [1]**	**Scores (general health and Tx-specific); HLA Match prior Conditioning**	**State of Disease prior Conditioning**
Patient Identification Number	Hodgkin lymphoma	**BMI** at TX and ID (kg/m²) (WHO)	Karnofsky Index (%)	Complete Remission
Sex (female; male)	Myeloic Neoplasms [3]	**Body Weight** at Tx and ID (in kilogram)	HCTCI- Score (1-10)	Aktive progressive
Date of Birth	High- grade Non-Hodgkin-Lymphoma/ acute lymphoblastic leukemia [4]	**Body Height** at Tx and ID (in meters)	HLA Match (10/10)	stable disease
Age at Transplantation (years)	Indolent Non Hodgkin Lymphoma	**BMI** at TX and ID (kg/m²)	HLA Mismatch (single; double = 9/10; <9/10)	aktive regressive
Date of Transplantation **d+0, d+30 and d+100** [2]	severe aplastic anemia	**BMI** (own measurement) **UW ≤19.9**	MRD, MUD, MiRD, MiUD	relapse prior Tx
Age at Initial Diagnosis (years)	ß-Thallasaemia	**BMI Δ** ID to Tx	**Conditioning Regime**	Pre-Therapies and Conditioning Schemes
Date of Initial Diagnosis			RIC	Infection parameter CMV (patient or donor positive/negative)
			MAC	Infection parameter CMV (patient or donor positive/negative)
legend: [1] The BMI according to the WHO criteria: UW: <18.5; NW ≥18.5-24.9; OW: ≥25-29-9; OB ≥30; [2] d+0= day of Tx; d+30= 30 days post Tx; d+100= 100 days post Tx; [3] acute myeloic leukemia, myelodysplastic syndrome, myeloproliferative diseases); [4]aggressive non Hodgkin lymphoma, acute lymphatic leukemia, lymphoblastic lymphoma;				

Table 2: Overview of all examined patient demographic data and the Transplantation setting (total cohort, part 1)

DETAILED CHART OF EXAMINED PARAMETERS (prior Conditioning, on d+30 and d+100: Total Cohort of n=461 Cases- Period of Data Collection: 1.1.2012-10.11.2017 PART 2 [1]						
Transplantation Course	***Survival Data and aGvHD-I***		**Laboratory Parameters and Scores**			
Stem Cell Information	**time interval (date TX to event (months or days))**	**Acute GvHD (≤ d+100)**	**Parameters of inflammation and nutritional status priorTx, d+30, d+100**	**hemogram and ratios on d+30 and d+100**	**Scores [3] (CNG and IMS d+30, d+100)**	**immune status, ratios on d+100_ *immune cells/CD34+ stem cells* [3]**
infused stem cells (per kg body weight (CD34+ cells))	OS (months)	Overall Severity aGvHD (I; II; III; IV) [2]	CRP in mg per dl	Lymphocytes in % to leukocytes	**CRP/Protein (PCR)**	T-Lymphocytes absolute
stem cell source (peripheral blood; bone marrow)	PFS (months)	Significant GvHD up to d+100: 1=yes (>=II°); 0=no (0 or I°)	Protein in g per l	Neutrophils in % to leukocytes	**CRP/Albumin (GPS)**	CD4+ Effector T cell (T-Helper-Cell) relative proportion
	NRM (months) and cause of death	time interval (days) TX to aGvHD **≥II°** (*significant* manifestation); alternatively, no aGvHD-I **≤I°**	Albumin in g per l	**Neutrophils/Lymphocytes Ratio**	**CRP/Albumin and NLR (CGN)**	CD8+ Regulatory T-Cells (Suppressor)relative proportion and absolute number
	RI (months) with n=240 in complete remission	Date Onset aGvHD (d+0; x; d+100)			**CRP/Protein and NLR (IMS)**	**CD4+/CD8+ Ratio**
		Date onset individual severest aGvHD				B-Lymphocytes relative ratio and absolute number (CD19+; CD20+)
		time interval (days) Tx to onset of aGvHD (grade-independent) during hospitalisation				CD16+/56+ Natural Killer T-Lymphocytes relative ratio and absolute number
		affected organ system (liver, skin, gastro-intestinal)				IL-2-R+ cells relative and absolute number
						CD3+ and HLA-DR positive active T-Lymphocytes relative and absolute number
legend: [1] see list of abbreviations; [2] see Oncopedia guideline: acute GvHD classification system; [3] see chapter below						

Table 3: Overview of all examined patient demographic data and the Transplantation setting (total cohort, part 2)

- Demographic data: sex, age at transplantation, body height and weight at initial diagnosis and prior conditioning, BMI at ID and prior TX categorized into 3 (4) groups according to WHO scheme, initial diagnosis, and diagnosis groups (haematological or oncological disease)

- HCT-CI score and the Karnofsky index prior TX

- Pre-therapies, conditioning schemes, CMV infection parameters and the disease status prior transplantation

- Information on the donor-receiver relationship: The CMV status, the HLA compatibility: match related/unrelated donor or a mismatch, the method of stem cell extraction (from the bone marrow or peripheral blood stem cells), the amount of CD34+ blood stem cells per kilogram of body weight

- Follow up until day 100 after allogeneic stem cell transplantation: Key date for the end of the follow up was the 10 November 2017. The incidence of an acute GvHD status was documented and categorized according to the "Oncopedia guidelines"; incidence, severity and affected organ were documented.

- Record of selected laboratory parameters: large blood count and typical inflammation parameters, immune status on days 30 and 100 after transplantation.

Based on available information on the BMI, patients were divided into four groups: Group UW was defined as Underweight patients, group NW as Normal weight patients, group OW as Overweight patients and group OB as Obese patients (see Table 4).

BMI Groups according to the WHO- Classification		
Groups	Classifikation	BMI (kg/m²)
UW	Underweight	<18
NW	Normalweight	≥18-24.9
OW	Overweight	≥25-29.9
OB	Obese	≥30

Table 4: BMI groups according to the definition of the WHO-Classification-System

The determination of the cut-off values was carried out according to the WHO definition. The case number ratio in the individual groups are representative of the BMI distribution in the overall population.

Glasgow-Prognostic-Score (GPS)

The Glasgow-prognostic-score (see Table 5) has been evaluated according to the definitionby Altay et al and Forrest et al: “patients with an increased CRP level (>1.0 mg/dL) and low albumin level (<3.5 g/dL) were assigned a GPS of 2. Patients with only one of these biochemical abnormalities were allocated a GPS of 1. Patients with neither of these abnormalities were assigned a GPS of 0” (Altay et al. 2019; Forrest et al. 2003; Forrest et al. 2005). Patients with only one of these abnormalities were allocated a score of 1a or 1b respectively. Values were collected within days upon start of the conditioning regimen and at day 30 and 100 post transplantation.

Glasgow Prognostic-Score (GPS)	**Albumin (g/l)**	**C-Reactive Protein (mg/l)**
GPS 0	≥35	≤10
GPS 1a	≥35	>10
GPS 1b	<35	≤10
GPS 2	<35	>10

Table 5: Glasgow Prognostic-Score (GPS) and corresponding Albumin and C-Reactive Protein values

Immuno-Metabolic-Score

The “Immuno-Metabolic-Score” was newly developed based on the scoring systems analysed in this thesis as a combination of the Protein-CRP-Ratio and the Neutrophil-Lymphocyte-Ratio. An NLR of 2 is selected, since the cut off of NLR >/< 2 was also defined for the CNG-Score (see Table 6).

Immuno-Metabolic-Score	Protein mg/l	C-reactive Protein mg/L	NLR
IMS 0	≥64	≤10	≤2
IMS 1a	<35	≤10	≤2
IMS 1b	≥35	>10	≤2
IMS 1c	≥35	≤10	>2
IMS 2a	<35	≤10	>2
IMS 2b	≥35	>10	>2
IMS 2c	<35	>10	≤2
IMS 3	<35	>10	>2

Table 6: Immunometabolic Score (IMS) and corresponding Protein, C-Reactive Protein and NLR

3.2 Statistical Methods

Statistical data analysis was performed using GraphPad Prism, Version 5.01© for Microsoft Windows. Statistical significance was assumed when p-values were <0.05. Descriptive statistics of demographic and clinical characteristics of the entire cohort of 461 patients were shown as absolute and relative frequency, median, mean values and 95%-confidence-intervals (CI).

3.2.1 Kaplan Meier Survival curves, Log-Rank test, p- value and hazard ratio

The Kaplan-Meier method was used to determine survival rates (i.e., OS, PFS, NRM) in distinct subgroups until data lock (10 November 2017). The date of allogeneic transplantation (day 0) served as the start of the observation period for each survival analysis. The defined endpoints were „death", "death by another cause other than relapse" or occurrence of an acute GvHD significant degree (≥2°). The data collected was sorted according to gender and BMI, furthermore the complete cohort was compared with the group of patients receiving reduced intensity conditioning (RIC) and matched HLA typing.

The overall survival (OS) was defined as the observation period from day of transplantation until completion of allogeneic transplantation to the end of the observation period in 2017 or death from any cause. The progression-free survival (PFS) marks the period from transplantation to relapse or disease progression. Non-relapse mortality (NRM) was specified as the period from Tx until the endpoint “death” without the occurrence of a relapse.

In order to test the significance of the Kaplan-Meier curves log-rank tests were performed, which test the independence of the graphs from possible confounding factors. The significance level is determined by the p-value, which calculates the likelihood of chance occurrence of the observed differences between groups. If the p-value was 0.05 or less, statistical significance was assumed. The likelihood of an event occurring within a particular group during a specific time period was determined by hazard. The hazard ratio is the comparison of two hazards, if the hazard ratio was greater than 1, the probability of an event was increased, if it was less than 1, the probability was decreased.

Liu et al. 2017 developed a score composed of the Glasgow-Prognostic- Score (GPS) and the Neutrophil-Lymphocyte-Ratio (NLR). The cut-off for NLR was set at ≤2/>2.

4 Results

4.1 Patient main characteristics (descriptive statistics)

The total cohort consisted of 461 patients. The distribution into BMI groups was as follows: 4.8% of patients were underweight, 48.6% normal weight, 31% overweight and 15.6% obese. The median BMI at initial diagnosis was 25.4 and varied from 16 to 56.5. Before transplantation, the median BMI was 24.6 with a range of 15.1-50.4. The median age at transplantation was 57 years (ranging 18-76 years).56.8% of patients were male. The initial diagnoses on the basis of which alloHSCT was indicated, were Hodgkin lymphoma, myeloid neoplasms with 62.7%, high grade non-Hodgkin lymphoma and acute lymphoblastic leukaemia, indolent non-Hodgkin lymphoma. On average, patients had a Karnofsky index of 90% (ranging from 30 to 100%) before transplantation., The mean HCT-CI-score (Hematopoietic cell transplantation-specific comorbidity index, definition see chapter 5.1) was 2 points. (see Table 7).

AlloHSCT was conducted under the following setting: 77.7% of patients received reduced intensity conditioning (RIC), almost 20% had myeloablative conditioning (MAC). 448 patients received peripheral blood stem cell transfusions, accounting for 97.2% of the total cohort. On average, patients received 6.7 million stem cells per kilogram of recipient's body weight (kgBW), ranging from 1.05 to 21.85 million CD34+ cells per kgBW. Almost 50% of the donors were matched unrelated donors (MUD), while 23.4% were matched unrelated donors (MRD) and 21.9% mismatched donors (see Table 7 "transplantation settings").

		BMI groups according to the WHO schema [1]			
Variables	**Total number of patients (n=461) (100%)**	**Underweight (n=22) (4.8%)**	**Normal weight (n=224) (48.6%)**	**Overweight (n=143) (31%)**	**Obese recipients (n=72) (15.6%)**
Body-Mass-Index (BMI) at Transplantation (TX) and Initial Diagnosis (ID)					
BMI-TX, median (min-max)	24.6 (15.1-50.4)	17.5 (15.1-18.5)	22.7 (18.7-24.9)	27.1 (25.0-29.9)	32.7 (30.0-50.4)
BMI-ID, median (min-max)	25.4 (16.0-56.5)	20.6 (16.0-34.4)	23.4 (18.1-33.6)	27.4 (19.2-34.8)	33.5 (25.5-56.5)
Age at Transplantation [years] median (min-max)	57 (18-76)	48 (18-63)	56 (18-75)	58 (19-76)	57 (24-75)
Gender, n (%)					
male	262 (56.8%)	7 (31.8%)	114 (50.9%)	97 (67.8%)	44 (61.1%)
female	199 (43.2%)	15 (68.2%)	110 (49.1%)	46 (32.2%)	28 (38.9%)
Diagnosis in groups, n (%)					
Hodgkin Lymphoma	12 (2.6%)	1 (4.5%)	8 (3.6%)	2 (1.4%)	1 (1.4%)
Myeloic Neoplasms [2]	289 (62.7%)	12 (54.5%)	128 (57.1%)	100 (70%)	49 (68.1%)
High-grade Non-Hodgkin Lymphoma/ Acute Lymphoblastic Leukemia [3]	92 (20%)	8 (36.4%)	55 (24.6%)	19 (13.3%)	10 (13.9%)
Indolent Non-Hodgkin Lymphoma [4]	60 (13%)	1 (4.5%)	28 (12.5%)	20 (14%)	11 (15.3%)
Others [5]	8 (1.7%)	0	5 (2.2%)	2 (1.4%)	1 (1.4%)
Karnofsky-Index [%], median (min-max)	90 (30-100)	90 (30-100)	90 (60-100)	90 (50-100)	100 (50-100)
HCT-CI Score, median (min-max)	2 (0-10)	2 (0-10)	2 (0-9)	2 (0-10)	3 (0-10)
TRANSPLANTATION SETTINGS					
Conditioning, n (%)					
Myeloablative Conditioning (MAC)	91 (19.7%)	4 (18.2%)	55 (24.5%)	22 (15.4%)	10 (13.9%)
Conditioning (RIC)	358 (77.7%)	17 (77.3%)	165 (73.7%)	117 (81.8%)	59 (81.9%)
Mini Conditioning [6]	12 (2.6%)	1 (4.5%)	4 (1.8%)	4 (2.8%)	3 (4.2%)
Method of Stem Cell Collection, n (%)					
Bone Marrow	13 (2.8%)	0	6 (2.7%)	4 (2.8%)	3 (4.2%)
Peripheral Blood Stem Cells	448 (97.2%)	22 (100%)	218 (97.3%)	139 (97.2%)	69 (95.8%)
Graft [x10^6/kg BW recipient], median (range)	6.7 (1.05-21.85)	7.68 (3.55-16.0)	7.46 (1.05-21.85)	6.35 (1.07-15.62)	5.37 (1.59-14.3)
Donors, n (%)					
Matched Related Donor (MRD)	108 (23.4%)	7 (31.8%)	56 (25%)	33 (23.1%)	12 (16.7%)
Matched Unrelated Donor (MUD)	228 (49.5%)	7 (31.8%)	105 (46.9%)	73 (51%)	43 (59.7%)
Mismatched Donor (8/10 and 9/10)	101 (21.9%)	5 (22.7%)	47 (21%)	33 (23.1%)	16 (22.3%)
Haplo	24 (5.2%)	3 (13.6%)	16 (7.1%)	4 (2.8%)	1 (1.2%)
Cytomegaly-Virology: Patient-Donor, n (%)					
Positive-Positive	194 (42.1%)	9 (40.9%)	91 (40.6%)	68 (47.6%)	26 (36.1%)
Positive-Negative	77 (16.7%)	3 (13.6%)	42 (18.8%)	24 (16.8%)	8 (11.1%)
Negative-Positive	40 (8.7%)	0	23 (10.3%)	11 (8%)	6 (8.3%)
Negative-Negative	149 (32.3%)	10 (45.5%)	68 (30.3%)	40 (28.0%)	31 (43.1%)
No Data	1 (0.2%)	0	0	0	1 (1.4%)

legend: [1]The BMI according to the World Health Organization (WHO) criteria: Underweight <18.5; Normalweight ≥18.5-24.9; Overweight ≥25-29.9; Obese ≥30; [2] acute myeloic lymphoma, myelodysplastic syndroma, myeloproliferative disease; [3] aggressive non hodgkin lymphoma, acute lymphatic leukemia, lymphoblasitc lymphoma; [4] chronic lymphatic leukemia; [5] severe aplastic anemia, hemoglobin disorders; [6] non-myeloablative conditioning

Table 7: Overview of all examined patient demographic data and the transplantation setting (total cohort, n=461)

The female cohort consisted of 199 patients, amounting to 43.2 percent of the total cohort. The BMI distribution was as follows: 7.5% underweight, 54.3% normal weight, 24.1% overweight and 14.1% obese. The average BMI was 24.6 at initial diagnosis and 23.5 before transplantation. On average, female patients were 56 years old at transplantation. 3.5% were diagnosed with Hodgkin lymphoma, 63.8% had myeloid neoplasm while 21.6% underwent transplantation due to high-grade Non-Hodgkin lymphoma or acute lymphoblastic leukaemia. On average, the women had a Karnofsky Index of 90%, ranging from 30 to 100%. On average, the HCT-CI score was 3. Regarding the transplantation procedure, almost 80% of the women received RIC, 18.6% received MAC while 193 of the 199 patients were transplanted with pBSC. The average amount of CD34+ stem cells was 7.03 million cells per kgBW and ranged from 2.81 to 19.98 million cells per kgBW. More than 50% had a MUD, almost 20% had a MRD. Mismatched donors amounted to 23.1% (see Table 8).

The male cohort consisted of 262 patients or 56.8% of the total cohort. 2.7% of men were underweight, 43.5% normal weight, 37% overweight and 16.8% obese. The average BMI was 26.1% (ranging from 16.8 to 56.5) at initial diagnosis and 25.5% (ranging from 16.8 to 50.4) before transplantation. The average age in the cohort was 57 years (range from 18 to 76 years old). 61.8% of patients were transplanted due to myeloid neoplasm, 1.5% had Hodgkin's lymphoma, 19.1% showed high-grade non-Hodgkin’s lymphoma or acute lymphoblastic leukaemia, 16% were diagnosed with low-grade Non-Hodgkin lymphoma or chronic lymphocytic leukaemia. The Karnofsky Index was 100% on average with a range of 50-100%. Most patients achieved an HCT-CI score of 2 points. Regarding the transplantation procedure, 76.7% underwent RIC, 21% had MAC. 255 out of 262 patients received pBSC as source of stem cells. On average 6.38 million CD34+ stem cells per kgBW were transfused, with a range of 1.05 to 21.85 million CD34+ cells per kgBW. Almost 50% of the donors were MUD, 27.1% MRD and 20.2% mismatched donors (see Table 9).

BASELINE PATIENT CHARACTERISTICS (female recipients n=199)					
		BMI group according to WHO schema [1]			
Variables	**Female Patients (n=199) (100%)**	**Underweight (n=15) (7.5%)**	**Normalweight (n=108) (54.3%)**	**Overweight (n=48) (24.1%)**	**Obese (n=28) (14.1%)**
Body-Mass-Index (BMI) at Initial Diagnosis (ID) and Transplantation					
BMI-TX, median (min-max)	23.5 (15.1-48.1)	17.7 (15.1-18.5)	22.1 (18.7-24.9)	26.9 (25.0-29.4)	33.1 (30.1-48.1)
BMI-ID, median (min-max)	24.6 (16.0-47.3)	20.3 (16.0-24.8)	22.7 (18.1-33.6)	27.4 (23.1-34.8)	33.5 (25.5-47.3)
Age at Transplantation [years], median (min-max)	56 (18-75)	46 (25-63)	57 (18-75)	58 (20-75)	55 (24-75)
Diagnosis in Groups, n (%)					
Hodgkin Lymphoma	7 (3.5%)	1 (6.7%)	5 (4.6%)	1 (2.1%)	0
Myeloic Neoplasms [2]	127 (63.8%)	9 (60%)	63 (58.3%)	33 (68.8%)	22 (78.6%)
High-grade Non Hodgkin Lymphoma/Acute Lymphoblastic Leukemia [3]	43 (21.6%)	4 (26.7%)	26 (24.1%)	9 (18.6%)	4 (14.3%)
Low-grade Non Hodgkin Lymphoma / Chronic Lymphocytic Leukemia [4]	18 (9.1%)	1 (6.7%)	11 (10.2%)	4 (8.3%)	2 (7.1%)
Others [5]	4 (2%)	0	3 (2.8%)	1 (2.1%)	0
Karnofsky- Index [%], median (min-max)	90 (30-100)	90 (30-100)	90 (60-100)	90 (80-100)	90 (70-100)
HCT-CI Score, median (min-max)	3 (0-10)	2 (0-6)	2 (0-8)	3 (0-10)	3 (0-9)
TRANSPLANTATION SETTINGS					
Conditioning, n (%)					
Myeloablative Conditioning (MAC)	37 (18.6%)	1 (6.7%)	28 (26%)	5 (10.4%)	3 (10.7%)
Reduced Intensity Conditioning (RIC)	157 (78.9%)	13 (86.7%)	79 (73.1%)	41 (85.4%)	24 (85.7%)
Mini Conditioning [6]	5 (2.5%)	1 (6.7%)	1 (0.9%)	2 (4.2%)	1 (3.6%)
Method of Stem Cell Collection, n (%)					
Bone Marrow	6 (3%)	0	5 (4.6%)	0	1 (3.6%)
Peripheral Blood Stem Cells	193 (97%)	15 (100%)	103 (95.4%)	48 (100%)	27 (96.4%)
Graft [x10^6/kg BW recipient] , median (range)	7.03 (2.81-19.98)	7.91 (5.17-16.00)	7.60 (2.81-19.98)	6.31 (3.0-12.9)	6.54 (3.23-14.3)
Donors, n (%)					
Matched Related Donor (MRD)	38 (19.1%)	4 (26.7%)	21 (19.4%)	10 (20.8%)	3 (10.7%)
Matched Unrelated Donor (MUD)	102 (51.3%)	5 (33.3%)	51 (47.2%)	27 (56.3%)	19 (67.9%)
Mismatched Donor (8/10 and 9/10)	46 (23.1%)	4 (26.7%)	26 (24.1%)	10 (20.9%)	6 (21.4%)
Haplo	13 (6.5%)	2 (13.3%)	10 (9.3%)	1 (2.1%)	0
Cytomegaly-Virology: Patient-Donor, n (%)					
Positive-Positive	86 (43.2%)	8 (53.3%)	42 (38.9%)	25 (52.1%)	11 (39.3%)
Positive-Negative	34 (17.1%)	2 (13.3%)	22 (20.4%)	7 (14.6%)	3 (10.7%)
Negative-Positive	20 (10.1%)	0	14 (13%)	2 (4.2%)	4 (14.3%)
Negative-Negative	59 (29.6%)	5 (33.3%)	30 (27.7%)	14 (29.2%)	10 (35.7%)

legend: [1]The BMI according to the World Health Organization (WHO) criteria: Underweight <18.5; Normalweight ≥18.5-24.9; Overweight ≥25-29.9; Obese ≥30; [2] acute myeloic lymphoma, myelodysplastic syndroma, myeloproliferative disease; [3] aggressive non hodgkin lymphoma, acute lymphatic leukemia, lymphoblasitc lymphoma; [4] chronic lymphatic leukemia; [5] severe aplastic anemia, hemoglobin disorders; [6] non-myeloablative conditioning

Table 8: Overview of examined patient demographic data and the transplantation setting (female cohort)

BASELINE PATIENT CHARACTERISTICS (male recipients n=262)					
		BMI groups according to the WHO schema [1]			
Variables	**Male Patients (n=262) (100%)**	**Underweight (n=7) (2.7%)**	**Normalweight (n=114) (43.5%)**	**Overweight (n=97) (37%)**	**Obese (n=44) (16.8%)**
Body-Mass-Index (BMI) atTransplantation (TX)and Initial Diagnosis (ID)					
BMI-TX, median (min-max)	25.6 (16.8-50.4)	17.3 (16.8-18.2)	23.1 (18.7-24.9)	27.4 (25.0-29.9)	32.2 (30.0-50.4)
BMI-ID, median (min-max)	26.1 (16.8-56.5)	21.6 (16.8-34.4)	23.7 (18.2-29.7)	27.4 (19.2-31.9)	32.9 (26.2-56.5)
Age at Transplantation [years], median (min-max)	57 (18-76)	32 (18-47)	56 (19-75)	57 (19-76)	58 (24-73)
Diagnosis in Groups, n (%)					
Hodgkin Lymphoma	4 (1.5%)	0	2 (1.7%)	1 (1%)	1 (2.3%)
Myeloic Neoplasms [2]	162 (61.8%)	3 (42.9%)	63 (55.3%)	69 (71.1%)	27 (61.4%)
High-grade Non Hodgkin Lymphoma/Acute Lymphoblastic Leukemia [3]	50 (19.1%)	4 (57.1%)	30 (26.3%)	10 (10.3%)	6 (13.6%)
Low-grade Non Hodgkin Lymphoma / Chronic Lymphocytic Leukemia [4]	42 (16%)	0	17 (14.9%)	16 (16.5%)	9 (20.5%)
Others [5]	4 (1.5%)	0	2 (1.7%)	1 (1%)	1 (2.3%)
Karnofsky- Index [%], median (min-max)	100 (50-100)	100 (90-100)	90 (70-100)	90 (50-100)	100 (50-100)
HCT-CI Score, median (min-max)	2 (0-10)	1 (0-3)	2 (0-9)	2 (0-6)	2 (0-10)
TRANSPLANTATION SETTINGS					
Conditioning, n (%)					
Myeloablative Conditioning (MAC)	55 (21%)	3 (42.9%)	27 (23.7%)	18 (18.6%)	7 (15.9%)
Reduced Intensity Conditioning (RIC)	201 (76.7%)	4 (57.1%)	85 (74.6%)	77 (79.4%)	35 (79.5%)
Mini Conditioning [6]	5 (1.9%)	0,0	2 (1.7%)	1 (1%)	2 (4.5%)
Method of Stem Cell Collection, n (%)					
Bone Marrow	7 (2.7%)	0	1 (0.9%)	4 (4.1%)	2 (4.5%)
Peripheral Blood Stem Cells	255 (97.3%)	7 (100%)	113 (99.1)	93 (95.9%)	42 (95.5%)
Graft [x10^6/kg BW recipient] , median (range)	6.38 (1.05-21.85)	5.74 (3.55-12.51)	7.3 (1.05-21.85)	6.35 (1.07-15.62)	4.98 (1.59-13.32)
Donors, n (%)					
Matched Related Donor (MRD)	71 (27.1%)	3 (42.9%)	36 (31.6%)	23 (23.7%)	9 (20.5%)
Matched Unrelated Donor (MUD)	127 (48.5%)	2 (28.6%)	51 (44.7%)	49 (50.5%)	25 (56.8%)
Mismatched Donor (8/10 and 9/10)	53 (20.2%)	1 (14.3%)	21 (18.4%)	22 (22.8%)	9 (20.5%)
Haplo	11 (4.2%)	1 (14.3%)	6 (5.3%)	3 (3.1%)	1 (2.3%)
Cytomegaly-Virology: Patient-Donor, n (%)					
Positive-Positive	108 (41.2%)	1 (14.3%)	47 (41.2%)	45 (46.4%)	15 (34.1%)
Positive-Negative	43 (16.4%)	1 (14.3%)	20 (17.5%)	17 (17.5%)	5 (11.4%)
Negative-Positive	20 (7.6%)	0	9 (7.9%)	9 (9.3%)	2 (4.5%)
Negative-Negative	90 (34.4%)	5 (71.4%)	38 (33.3%)	26 (26.8%)	21 (47.7%)

legend: [1]The BMI according to the World Health Organization (WHO) criteria: Underweight <18.5; Normalweight ≥18.5-24.9; Overweight ≥25-29.9; Obese ≥30; [2] acute myeloic lymphoma, myelodysplastic syndroma, myeloproliferative disease; [3] aggressive non hodgkin lymphoma, acute lymphatic leukemia, lymphoblasitc lymphoma; [4] chronic lymphatic leukemia; [5] severe aplastic anemia, hemoglobin disorders; [6] non-myeloablative conditioning

Table 9: Overview of examined patient demographic data and the transplantation setting (male cohort)

4.2 Subgroup analysis: Pre-sorted baseline characteristics of homogeneous cohort comprising RIC, 10/10 HLA and pBSC as stem cell source (n=251)

Out of 251 patients, we developed a subgroup with homogeneous characteristics: These patients all received RIC, had only MUD and MRD donors, and the stem cell source was pBSC and 10/10 HLA. In the following, in the homogeneous cohort underweight patients were excluded. The distribution among the selected cohort was40.2% female and 59.8% male patients. On average, patients had a BMI of 25.3, ranging from 18.7 to 45.7. Women had an average BMI of 25,0, while men had 25.9. 45.4% of patients were normal weight, 36.7% overweight and 17.9% obese. The cohort had a mean age of 58 years, spanning from 24 to 75 years in females and 29 to 76 years in males. 73.3% of patients were transplanted due to myeloid neoplasms, of which the percentage in women was 76%. 10.8% had a high-grade non-Hodgkin lymphoma or acute lymphoblastic leukaemia, 14.8% had indolent non-Hodgkin lymphoma. On average, patients received 6.8 million CD34+ stem cells per kgBW, ranging from 2.0-21.85 million cells per kgBW. Before transplantation, 53.8% of patients were in complete remission, 12% showed active progressive disease, 13.5% were active regressive and 20.7% in stable disease. Almost 71% had a MUD. (see Table 10).

PRESORTING: reduced- intensity- conditioning; MRD & MUD; 10/10 HLA; pBSCT; NW/OW/OB			
VARIABLES	**all patients (n=251) (100%)**	**female patients (n=101) (40.2%)**	**male patients (n=150) (59.8%)**
BASELINE PATIENT CHARACTERISTICS			
body-mass-index (BMI) at transplantation (TX), median (range) [1]	25.3 (18.7-45-7)	25.0 (18.7-45.7)	25.9 (18.8-43.3)
normalweight (NW), n (%) [1]	114 (45.4%)	50 (49.5%)	64 (42.7%)
overweight (OW), n (%) [1]	92 (36.7%)	32 (31.7%)	60 (40.0%)
obese (OB), n (%) [1]	45 (17.9%)	19 (18.8%)	26 (17.3%)
age at TX [years], median (range)	58 (19-76)	58 (24-75)	58 (19-76)
DIAGNOSIS IN GROUPS, n (%)			
hodgkin lymphoma	2 (0.008%)	1 (0.01%)	1 (0.007%)
myeloic neoplasms [2]	184 (73.3%)	77 (76.2%)	107 (71.3%)
high-grade non hodgkin lymphoma/acute lymphoblastic leukemia [3]	27 (10.8%)	12 (11.9%)	15 (10.0%)
indolent non hodgkin lymphoma	37 (14.8%)	10 (9.9%)	27 (18.0%)
severe aplastic anemia	1 (0.004%)	1 (0.01%)	0
graft [CD34+ stem cellsx10^6/kg BW recipient] , median (range)	6.8 (2.0-21.85)	6.72 (3.23-19.98)	6.85 (2.0-21.85)
REMISSION STATUS PRIOR TX, n (%)			
complete remission (CR)	135 (53.8%)	56 (55.4%)	79 (52.7%)
active progressive diesase	30 (12.0%)	8 (7.9%)	22 (14.7%)
active regressive disease	34 (13.5%)	15 (14.8%)	19 (12.7%)
active stable diesase	52 (20.7%)	22 (21.7%)	30 (20.0%)
TX SETTING: DONORS, n (%)			
matched related donor (MRD) 10/10	73 (29.1%)	24 (23.8%)	49 (32.7%)
matched unrelated donor (MUD) 10/10	178 (70.9%)	77 (76.2%)	101 (67.3%)
legend: [1] The BMI according to World Health Organization (WHO) criteria: NW: 18.5–24.9; OW: 25.0–29.9; OB: ≥30.0; [2] acute myeloic lymphoma, myelodysplastic syndrome, myeloproliferative diseases; [3]aggressive non hodgkin lymphoma, acute lymphatic leukemia, lymphoblastic lymphoma			

Table 10: Homogeneous cohort (n=251): Overview of all examined patient demographic data and the Transplantation setting

4.3 Clinical Outcome of total cohort according to the BMI: OS, NRM, PFS and Incidence of aGVHD

A total of 461 cases were included in this analysis. Firstly, the cohort was examined in total as well as categorized to sex. Secondly, a homogeneous patient collective was established containing patients who received RIC and matched HLA with pBSC (n=251). This subgroup was also categorized by sex.

In the first instance, we analysed the data according to BMI-dependent survival. For this reason, the total cohort was categorised into the BMI groups normalweight (NW), overweight (OW) and obese (OB). The results were described for all groups as well as separately for the female and male groups.

Compared to different BMI groups, the OW had the best 5-year-survival and PFS, lowest NRM and lowest occurrence of an aGvHD. The OB had the highest incidence of an aGvHD and the most-probable death by relapse. A median overall survival of 21 months was observed in the NW as opposed to22 months in the OB. After 5 years, nearly 60% of the OW were still alive, whereas the survival in the NW and OB was about 30%. At 100 days after transplantation, 52% of OB developed a significant GvHD in contrast to 38.46% of NW and 40.56% of OW (see Figure 3).

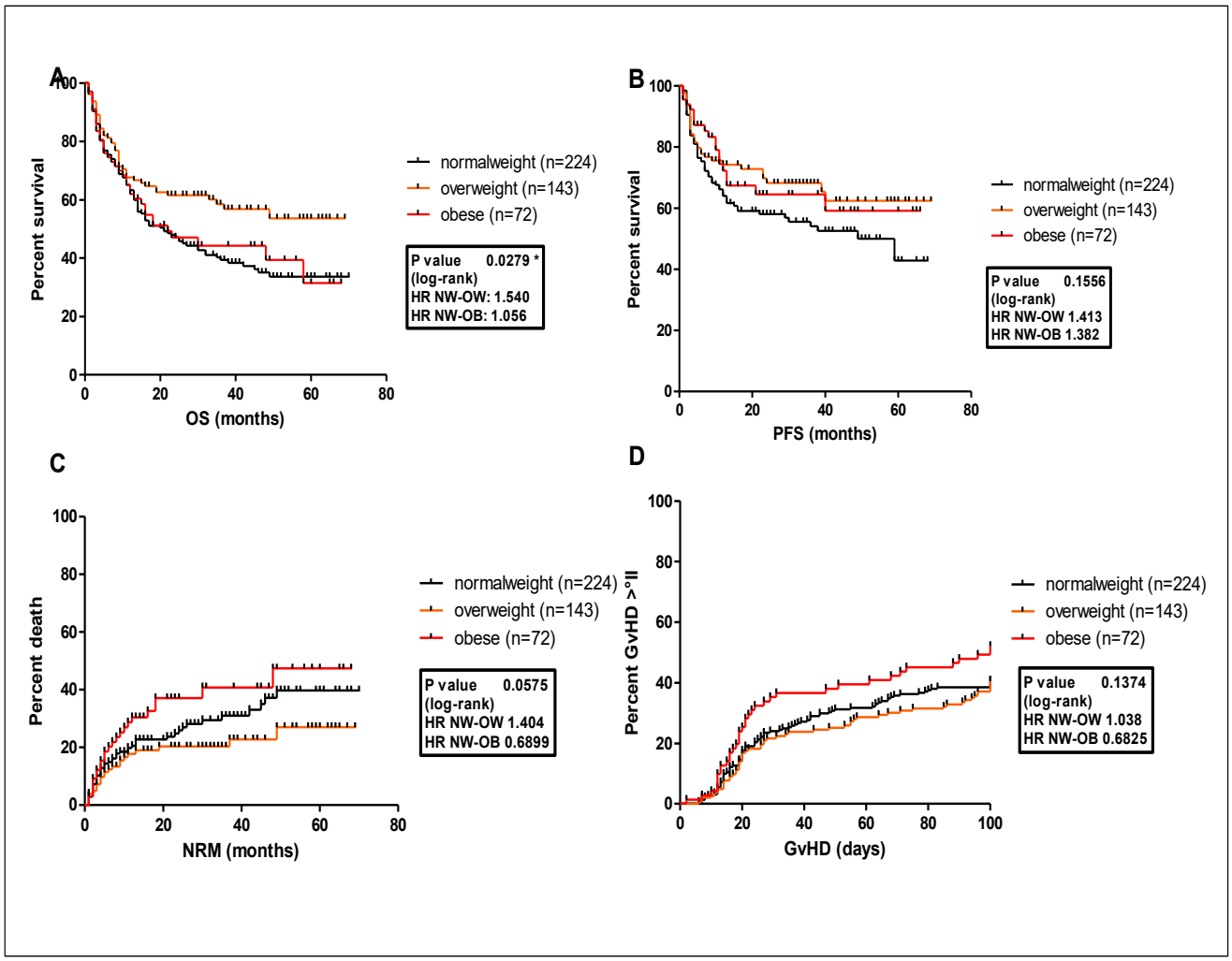


Figure 3: OS, PFS, NRM and aGvHD analysed by BMI and all recipients (without UW): A Overall Survival (OS) of 439 patients according to BMI (³18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²); B Progression Free Survival (PFS) of 439 patients according to BMI; C Non-Relapse-Mortality (NRM) of 439 patients according to BMI; D acute Graft-versus-Host-disease (aGvHD) of 439 patients according to BMI.

Figure 4 depicts the distribution of all weight groups including underweight. Recent research has shown being underweight had a special influence on survival after stem cell transplantation: Two studies, (Navarro et al. 2010) and (Thyagarajan et al. 2010), announced that cachectic patients with the lowest weight in each cohort had the worst survival, even worse compared with obese patients (Blanc et al. 2003) . The overall survival (OS) analysis revealed that after 43 months none of the 25 UW had survived, whereas 37% of the NW and over 50% of the OW/OB patients were alive. The median survival for UW was 12 months, for NW 21 months and OW/OB 49 months. The NRM showed that all UW died due to relapse after 43 months, about 70% of the OW/OB were alive or the cause of death was not related to relapse. For this reason, we excluded the underweight patient cohort from the following analyses.

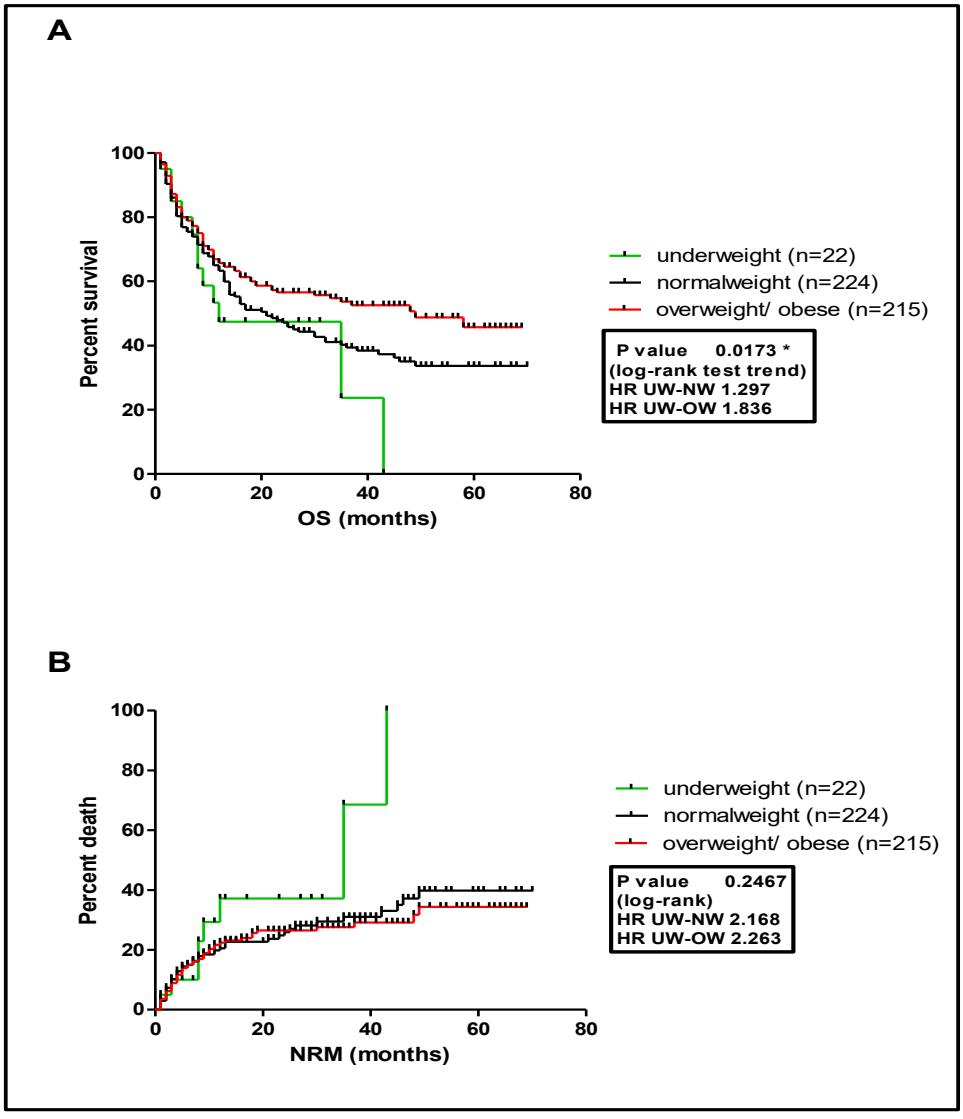


Figure 4: Analysis of OS and NRM via BMI: complete cohort including underweight patients: A OS of 461 patients according to the BMI (underweight <18.5; normalweight ³18.5 to <25 kg/m², overweight/obese ³25 kg/m²); B NRM of 461 patients according to the BMI groups.

In the female cohort, the overweight subgroups OW and OB had improved survival results. In contrast to NW and OW, the OB had the highest aGvHD-I, OW the lowest. In the OS, a median survival of 17 months was observed in the NW, and a median survival of 35 months in the OW (see Figure 5).

In the male cohort, only the OW had improved survival results, the OB and NW had a worse survival. OB were more likely to have a relapse-caused-death. In the OS, a median survival of 22 months was observed in the NW, and a median survival of 18 months in the OB. After 60 months, circa 60% of the OW were still alive, 33 % of the NW and 20 % of the OB. The acute GvHD incidence in the male groups revealed no significant differences after 100 days (see Figure 6).

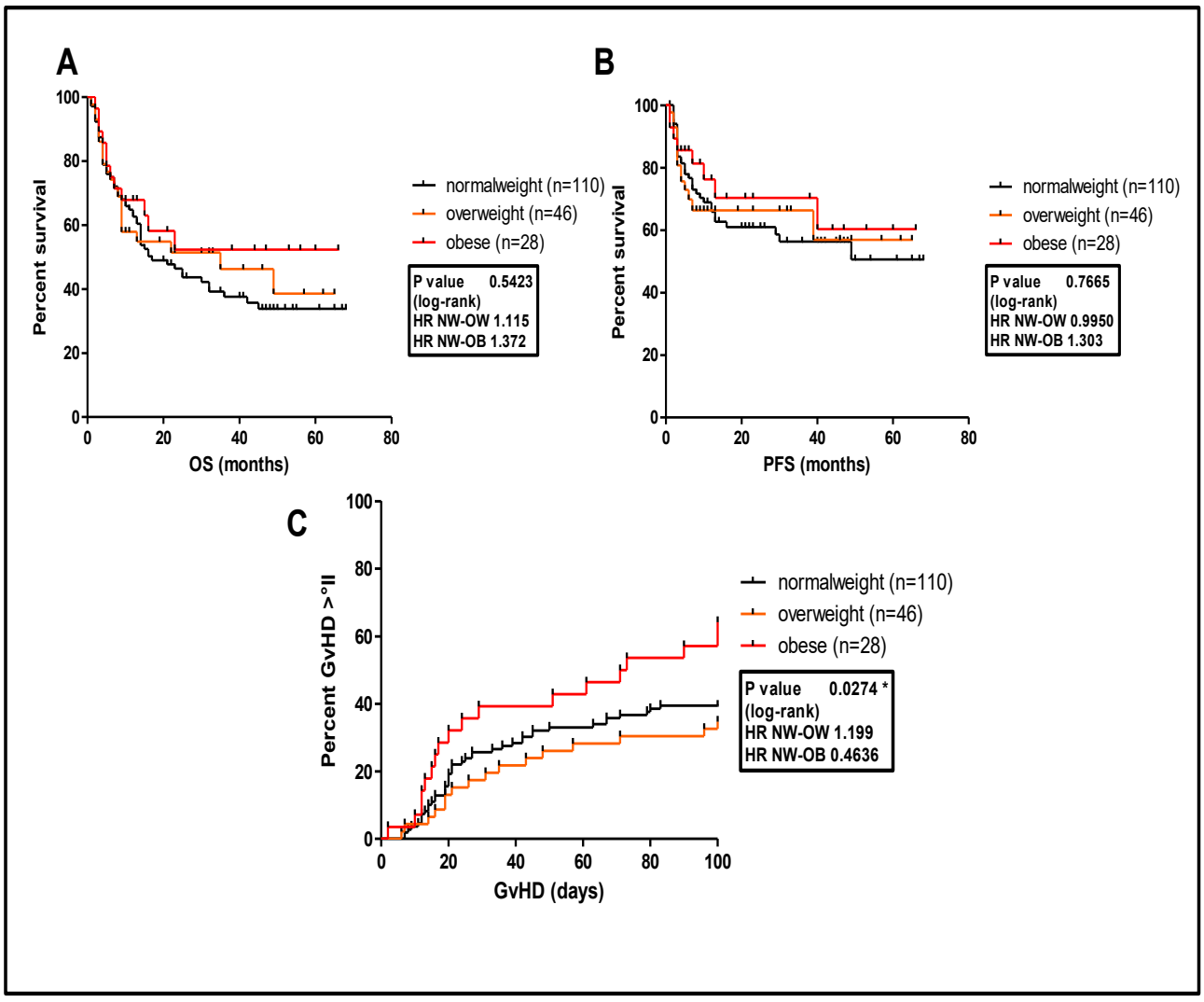


Figure 5: Survival outcomes of complete female cohort analysed by BMI (n=184), no UW: A Overall Survival (OS) of 184 female patients according to BMI (³18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²); B Progression Free Survival (PFS) of 184 female patients according to BMI; C acute Graft-versus-Host-disease (aGvHD) of 184 female patients according to BMI.

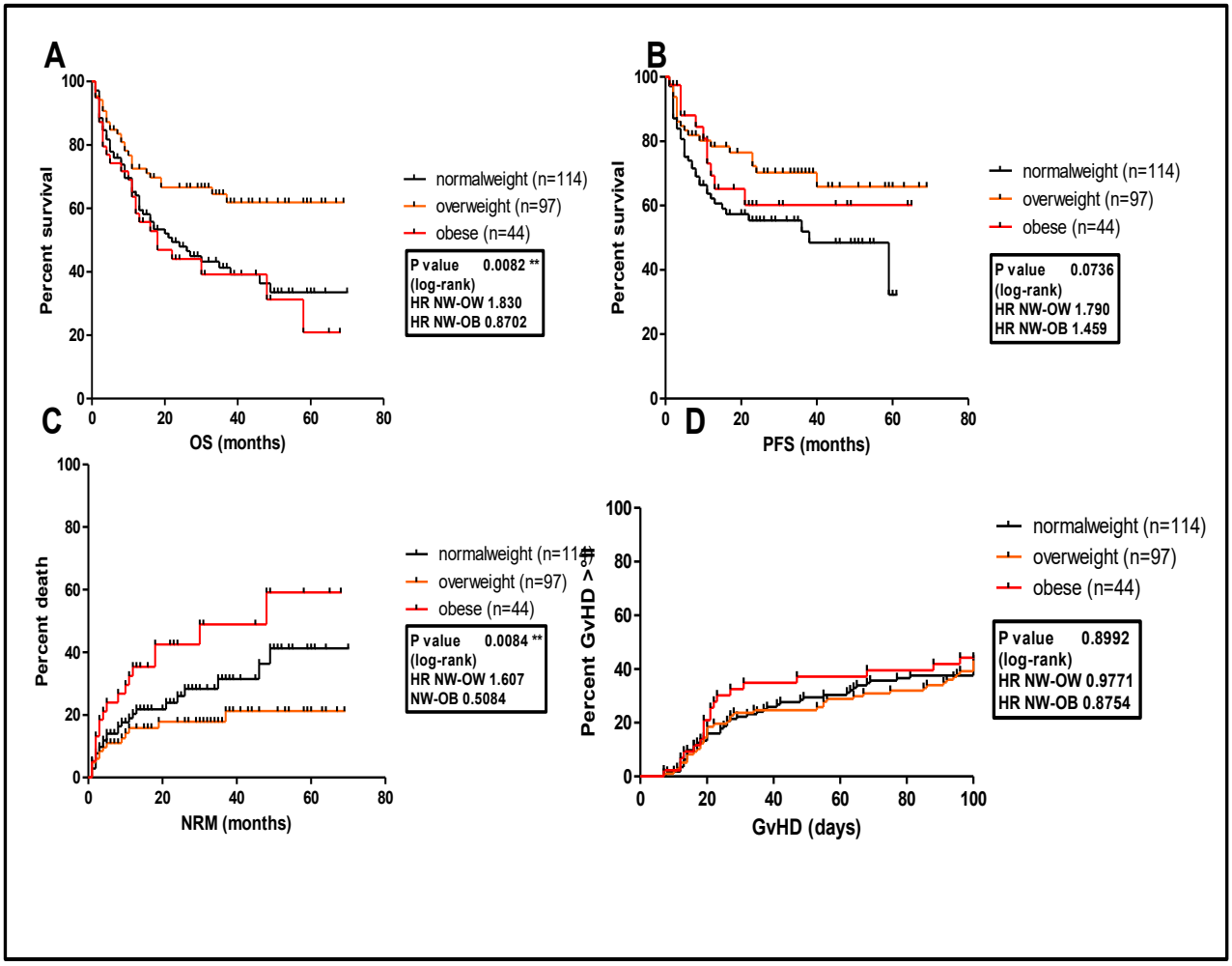


Figure 6: Survival outcomes of complete male cohort analysed by BMI (n=255), no UW: A Overall Survival (OS) of 255 male patients according to BMI (³18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²); B Progression Free Survival (PFS) of 255 male patients according to BMI; C Non-Relapse Mortality (NRM) of 255 male patients according to BMI; D acute Graft-versus-Host-disease (aGvHD) of 255 male patients according to BMI.

4.4 Clinical outcome according to BMI in the subgroup with RIC, 10/10 HLA and pBSC as stem cell source (n=251)

Continuing the analyses with the total cohort, we conducted the same analyses for the homogeneous subgroup with reduced intensity conditioning, 10/10 HLA and peripheral blood stem cells as stem cell source. In this cohort, the OW had significantly improved survival and NRM results. In the OS, a median survival of 23 months was observed in the NW, and a median survival of 30 months in the OB. After 60 months nearly 60% of the OW were still alive and only half as many of the NW and OB. Within 100 days, obese patients almost twice as often developed a GvHD in comparison to the other groups (see Figure 7).

In the female cohort, OW and OB patients had a better 5-year-survival and a higher aGvHD-I, especially OB patients developed twice as high GvHD incidences as the other groups. In the OS, a median survival of 17 months was observed in the NW, and a median survival of 49 months in the OW (see Figure 8).

In the male cohort, only the OW had significantly better survival results in the OS and NRM. In the OS, a median survival of 26 months was observed in the NW, and a median survival of 30 months in the OB. After 60 months, more than 65% of the OW were still alive, 33% of the NW and 25% of the OB. 100 days after transplantation, the OB had most significant GvHD, the NW nearly 40% and 30% of the OW (see Figure 9).

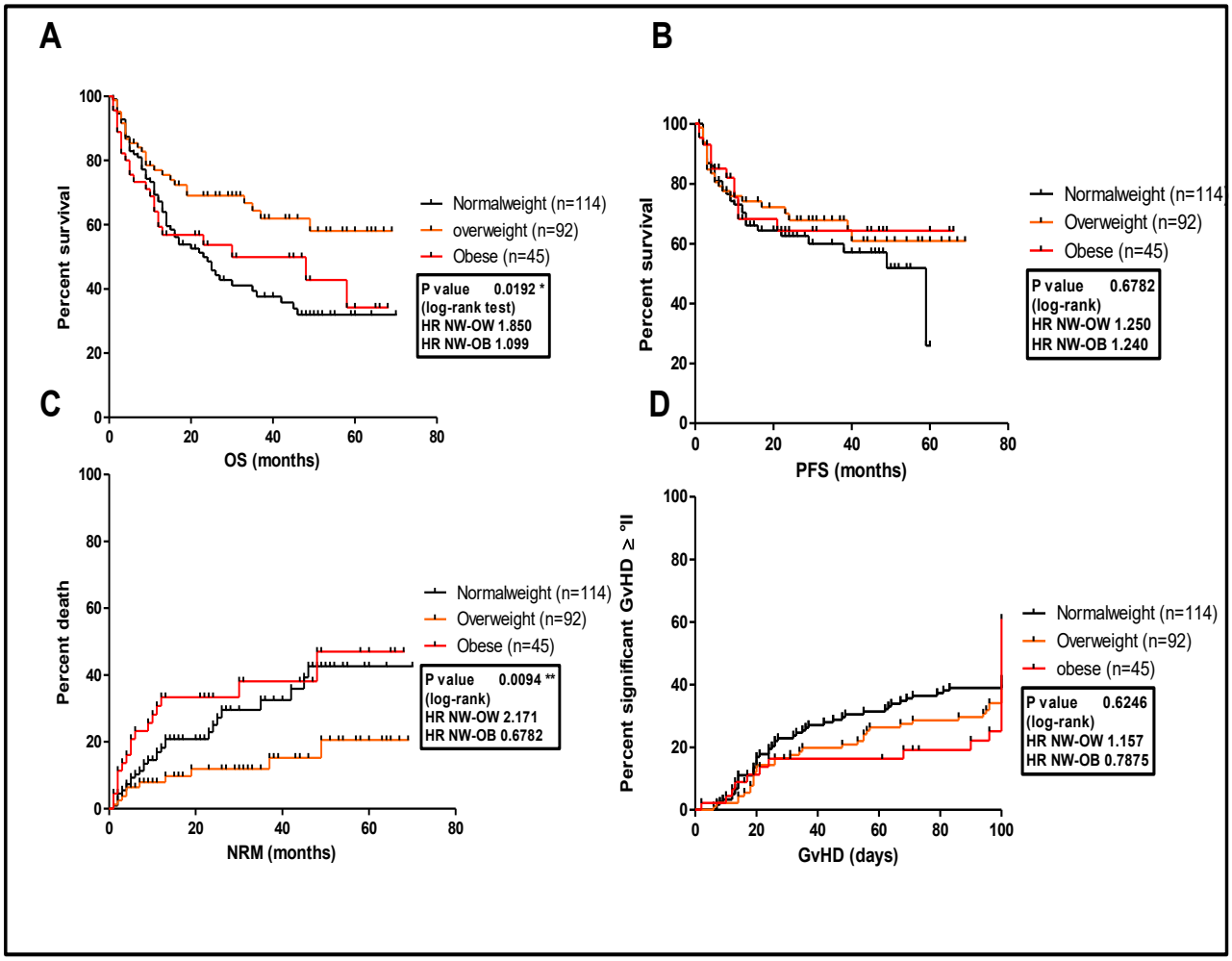


Figure 7: Survival outcomes of complete subgroup (RIC) analysed by BMI (n=251), no UW : A Overall Survival (OS) of 251 patients according to BMI (³18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²); B Progression Free Survival (PFS) of 251 patients according to BMI; C Non-Relapse Mortality (NRM) of 251 patients according to BMI; D acute Graft-versus-Host-disease (aGvHD) of 251 patients according to BMI.

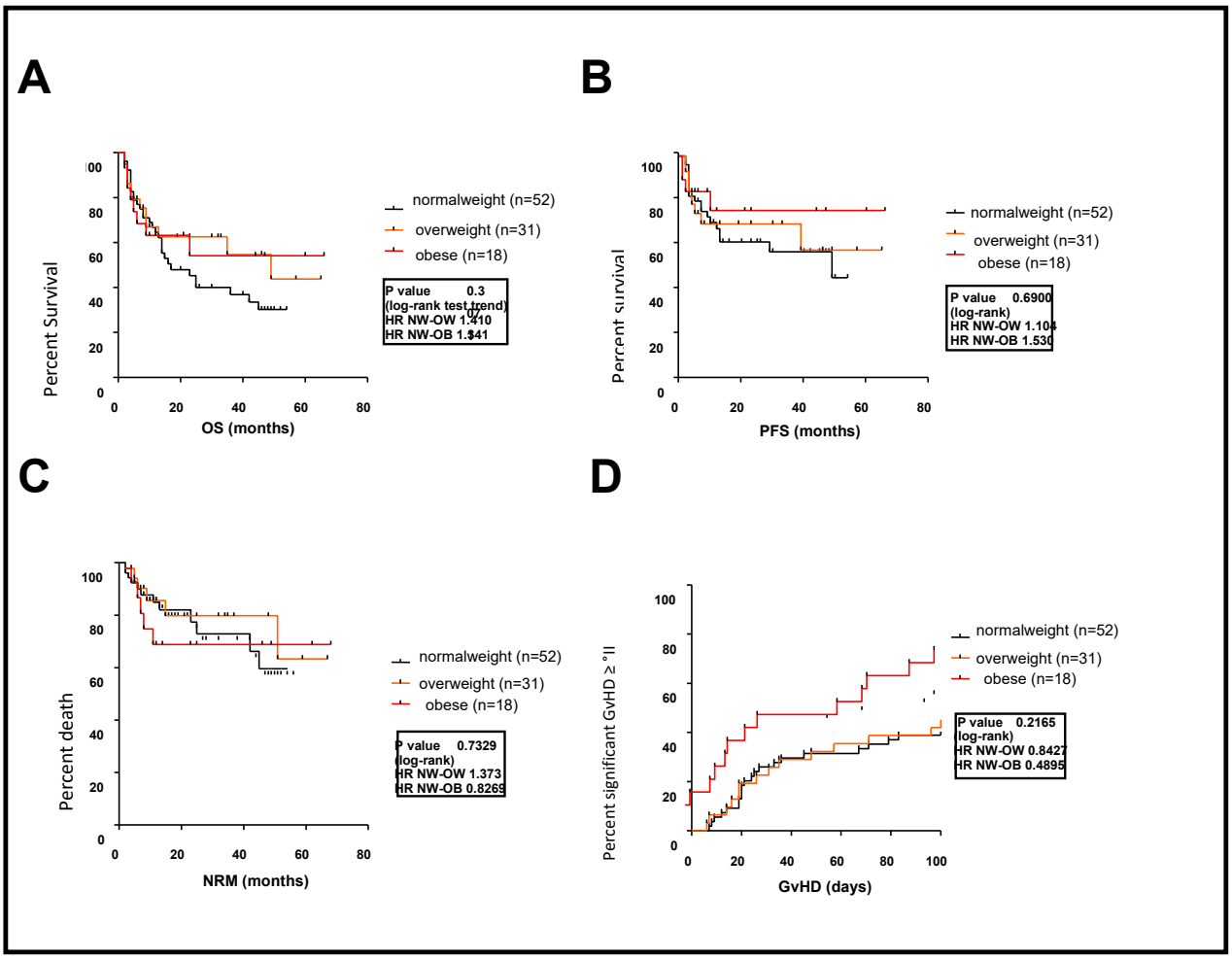


Figure 8: Survival outcomes of female subgroup analysed by BMI (n=101), no UW: A Overall Survival (OS) of 101 female patients according to BMI (18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²), B Progression Free Survival (PFS) of 101 female patient according to BMI; C Non- Relapse Mortality (NRM) of 101 female patient according to BMI; D acute graft-versus-host-disease (aGvHD) of 101 female patients according to BMI.

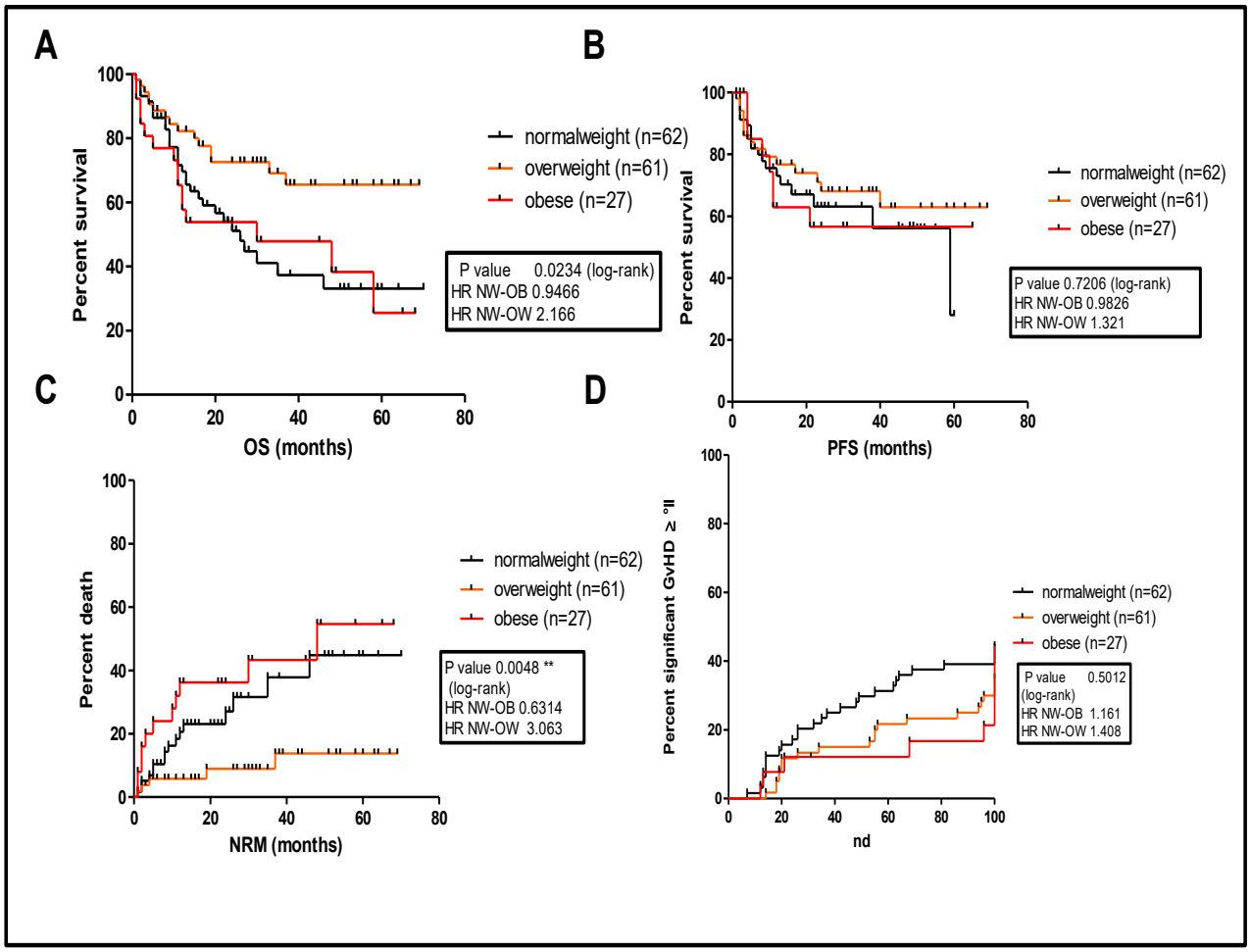


Figure 9: Survival outcomes of the male subgroup by BMI (n=150): A Overall Survival (OS) of 150 male patients according to BMI (³18.5 to <25 kg/m², ³25 to 30kg/m², ³30kg/m²); B Progression Free Survival (PFS) of 150 male patients according to BMI; C Non-Relapse Mortality (NRM) of 150 male patients according to BMI; D acute Graft-versus-Host-disease (aGvHD) of 150 male patients according to BMI.

4.5 Clinical outcomes according to immuno-metabolic scores GPS, NLR and IMS

Following the BMI-dependent analyses, we performed analyses on the total cohort and the homogeneous subgroup using the Glasgow Prognostic Score.

4.5.1 Clinical outcomes according to GPS pre-Tx

Firstly, OS, PFS, NRM and aGvHD incidence were analysed according to GPS groups. The laboratory values, CRP and albumin, were measured before transplantation. The median OS in the GPS 0 was 35 months, 30 in the GPS 1 and the GPS 2 survived 21 months. The 5-year OS in the GPS 0, 1 and 2 was 40.7%, 34.6% and 35.3%, respectively. For OS, PFS, NRM and acute GvHD incidence, there were no significant differences in the cohort (see Figure 10)

In the homogeneous subgroup with RIC and matched HLA, the median survival in the GPS 0, 1 and 2 was 49, 26 and 19 months, respectively. The 5-year- OS was 45.2% in the GPS 0, 28.8% in the GPS 1(a and b) and 41.3% in the GPS 2. The NRM was 68.2% in the GPS 0, 42.7% in the GPS 1a and 86.9% in the GPS 1b, 58.4% in the GPS 2. Within 100 days, 38.4% of the GPS 0 developed a significant aGVHD, 34.1% of the GPS 1a and each 50% in the GPS 1b and 2 (see Figure 11).

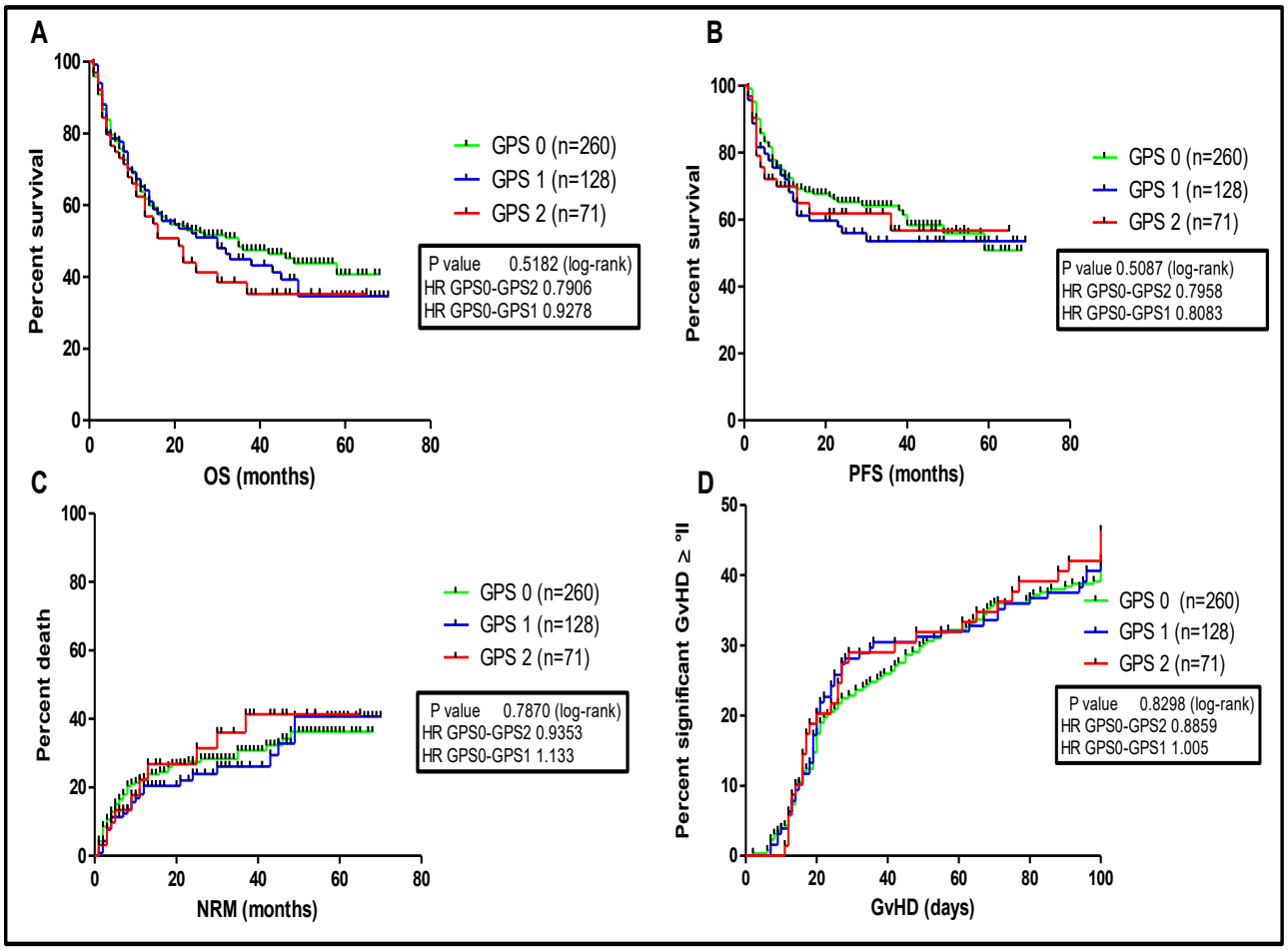


Figure 10: Survival results analysed by "original GPS" pre-Conditioning Regimen (pre-Tx) with all recipients, n=459 A Overall Survival (OS) of 459 patients according to GPS B Progression Free Survival (PFS) of 459 patients according to GPS; C Non-Relapse Mortality (NRM) of 459 patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 459 patients according to GPS.

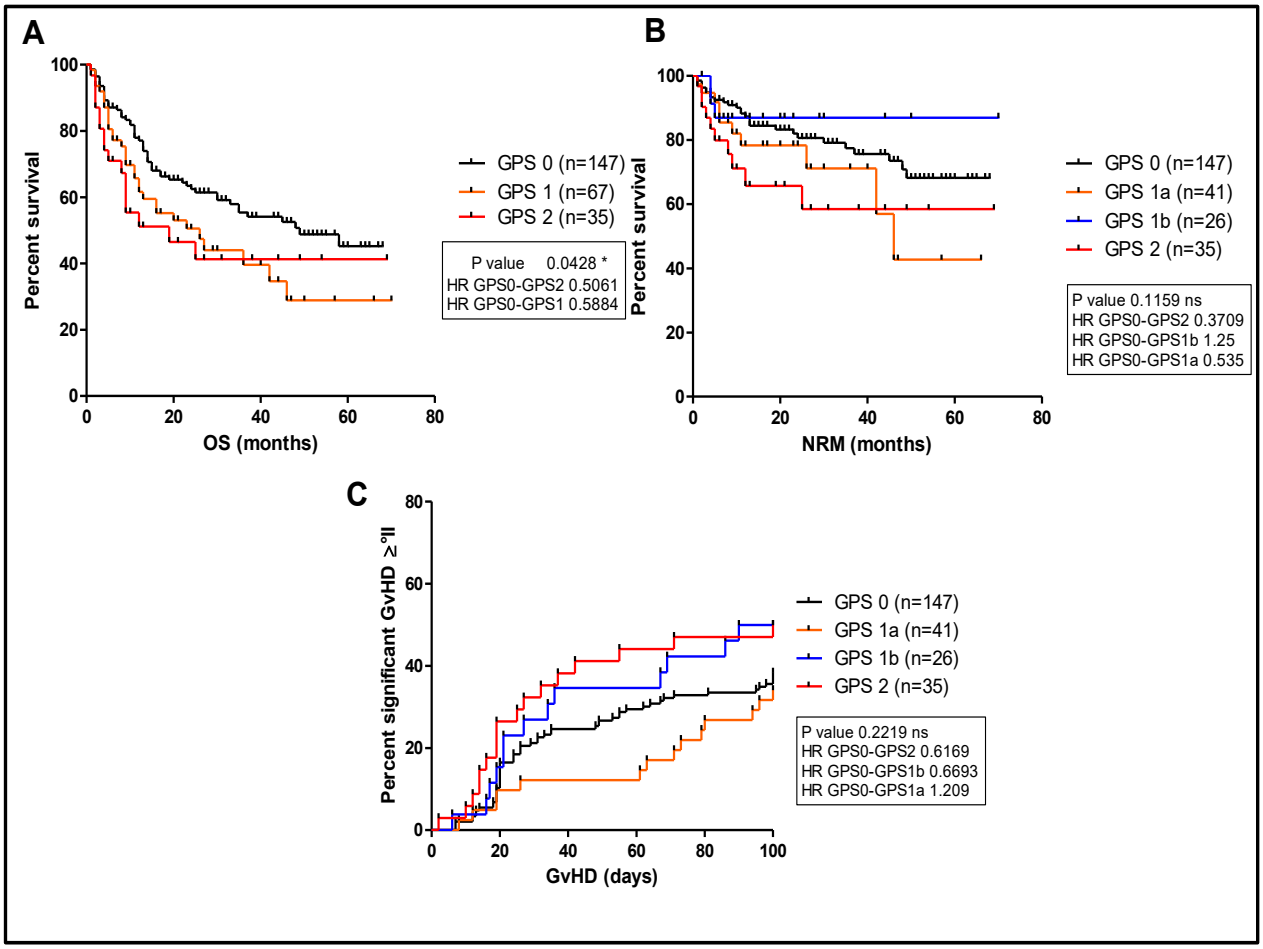


Figure 11: Survival results analysed by "modified GPS" pre-Conditioning Regimen (pre-Tx) with all recipients, no UW: A Overall Survival (OS) of 249 patients according to GPS, RIC and matched HLA B Non-Relapse Mortality (NRM) of 249 patients according to GPS; C acute Graft-versus-Host-disease (aGvHD) of 249 patients according to GPS.

4.5.2 Clinical outcomes according to GPS on d+100

The poorest 5-year-survival and NRM results had the GPS 2. There were no major differences in survival among the remaining groups. In the OS, a median survival of 20 months was observed in the GPS 0, 14 months in the GPS1b and 8 months in the GPS 2 (see Figure 12).

Female patients with inflammation and malnutrition characteristics, corresponding to GPS 2, had the worst survival and NRM results. In comparison, the GPS 0 had the best survival and 100% survival in the NRM. In the OS, a median survival of 7 months was observed in the GPS 2. After 60 months 66% of the GPS 0 were still alive, 52% of the GPS 1 and 10% of the GPS 2 (47 months) (see Figure 13).

In the male cohort, worst survival parameters were shown by the GPS 2, patients with malnutrition and inflammation. In the OS, a median survival of 8 months was observed in the

GPS 2, 19 months for the GPS 0 and 16 months for the GPS 1a. After 60 months 32% of the GPS 0 were still alive, 7% of the GPS 2, 63.49% of the GPS 1b (46 months) and 33.3% of the GPS 1a (38 months) (see Figure 14).

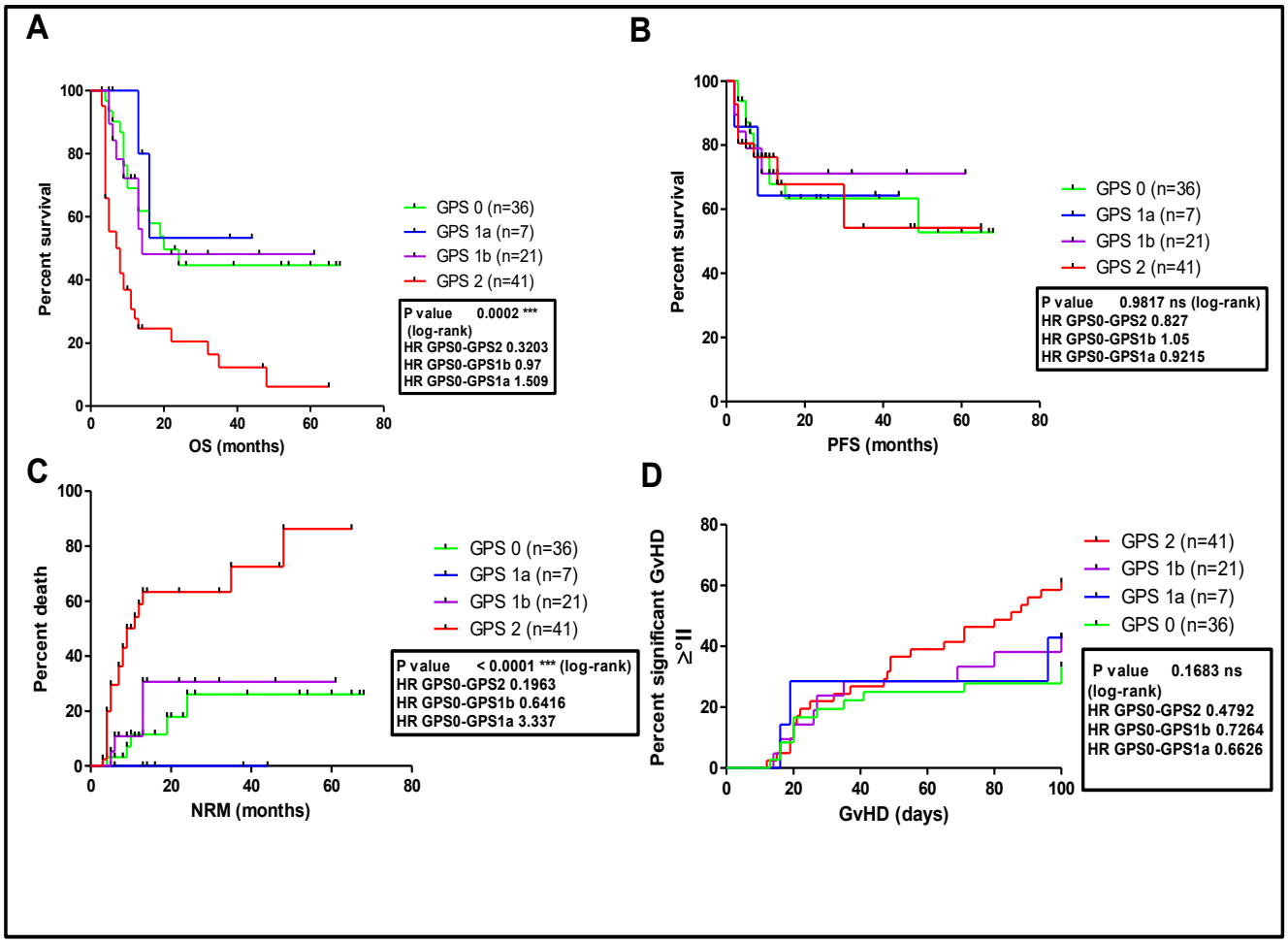


Figure 12: Survival results analysed by "modified GPS" on d+100 with all recipients, no UW, n=105: A Overall Survival (OS) of 105 patients according to GPS B Progression Free Survival (PFS) of 105 patients according to GPS; C Non-Relapse Mortality (NRM) of 105 patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 105 patients according to GPS.

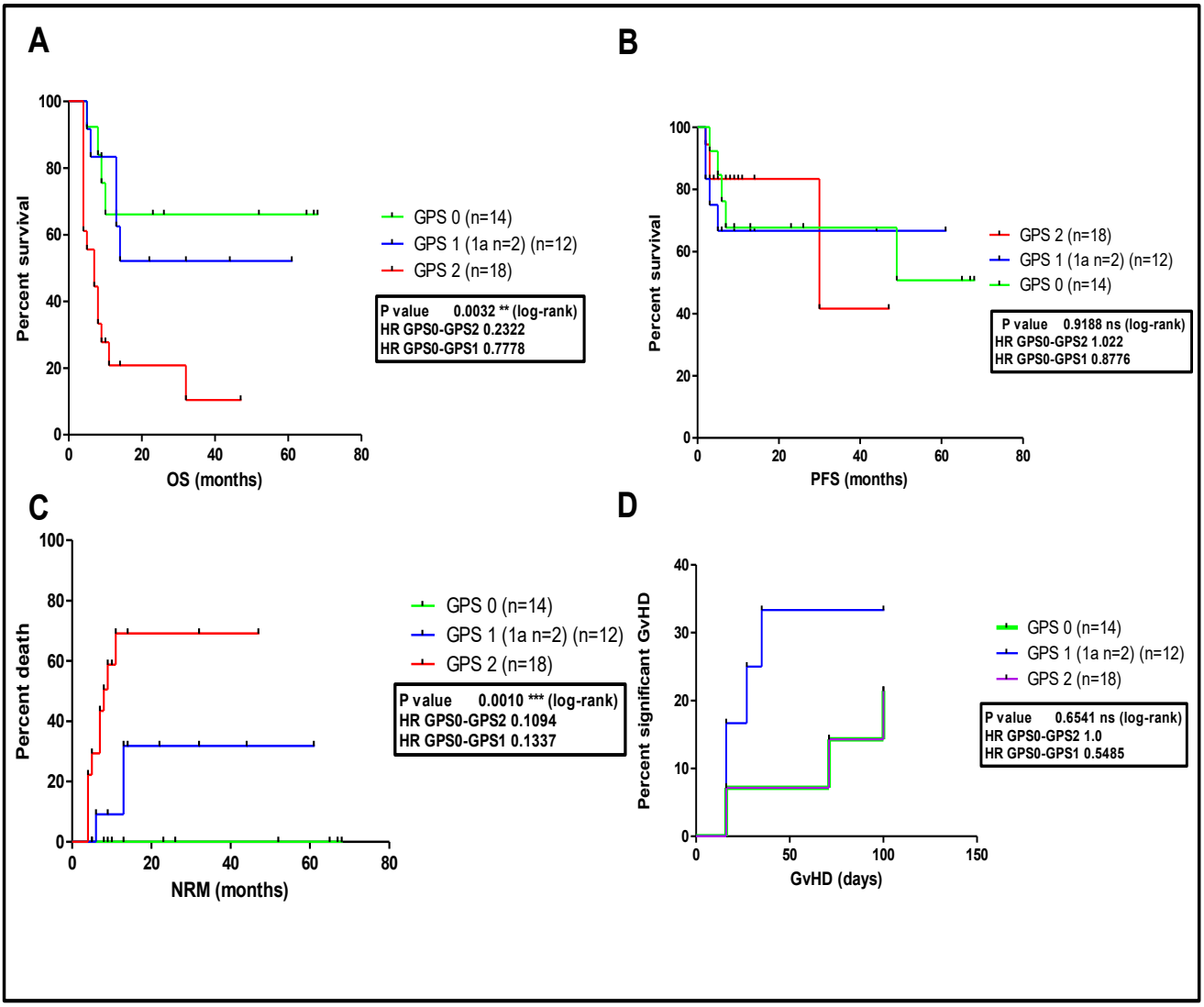


Figure 13: Survival results analysed by "original GPS" on d+100 with female recipients, no UW, n=44: A Overall Survival (OS) of 44 female patients according to GPS B Progression Free Survival (PFS) of 44 female patients according to GPS; C Non-Relapse Mortality (NRM) of 44 female patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 44 female patients according to GPS.

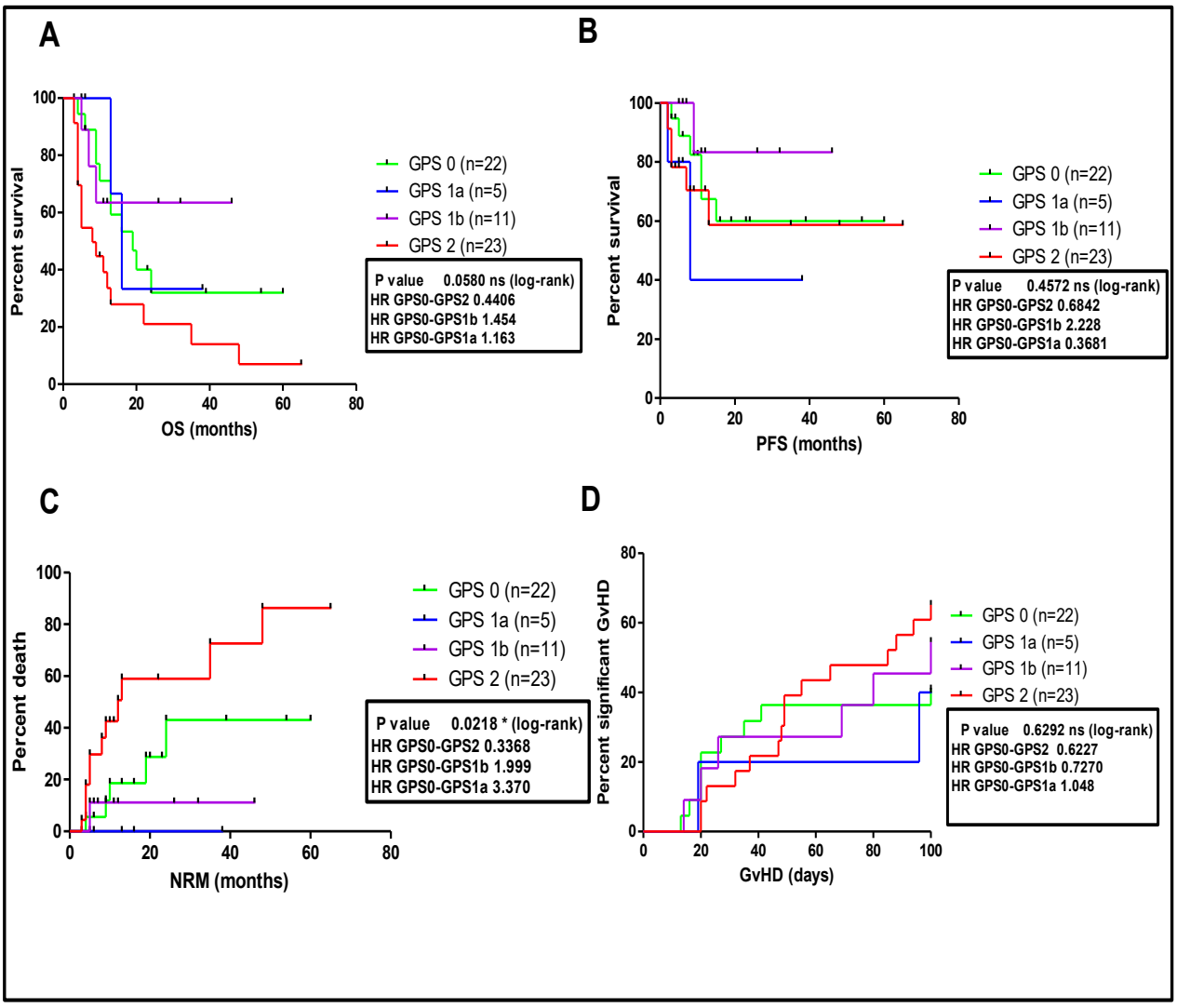


Figure 14: Survival results analysed by "modified GPS" on d+100 with male recipients, no UW, n=61: A Overall Survival (OS) of 44 female patients according to GPS B Progression Free Survival (PFS) of 44 female patients according to GPS; C Non-Relapse Mortality (NRM) of 44 female patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 44 female patients according to GPS

4.5.3 Clinical outcomes according to GPS on d+100: subgroup analysis with RIC, 10/10 HLA and pBSC

The median survival in the GPS 0 is 24 months, 38 months in the GPS 1a, 13 months in the GPS 1b and 8 months in the GPS 2. After 60 months, 45.25% of the GPS 0 are still alive, 50% of the GPS 1a after 44 months, 40.4% of the GPS 1b after 32 months and after 48 months, there are no survivors in the groups of GPS 2. A progression free life had 35.7% of the GPS 0 after 60 months. 55.5% of the GPS 1a are progression-free up to month 44, 65.45% of the GPS 1b after 26 months and 80% of the GPS 2 after 48 months. These are the results of the NRM: 66.37% of the GPS 0 after 60 months. 100% of the GPS 1a after 44 months, 53.87% of the GPS 1b after

32 months and 0% of the GPS 2 after 48 months. A significant aGvHD is developed by 29.41% of the GPS 0 within 100 days, by 50% of the GPS 1a, 46.15% of the GPS 1b and by 60% of the GPS 2. The GPS 2 which are characterized by malnutrition and inflammation have by far the worst survival and aGvHD incidence (see Figure 15).

There is a median survival of 13 months in the group of GPS 1 and 7 months in the GPS 2. This was not measurable for the GPS 0. OS distribution: After 52 months, there are still 66.6% of the GPS 0 alive, 44.4% of the GPS 1 after 44 months and 20.52% of the GPS 2 after 47 months. There are no more progression-free survivors in the groups GPS 0 after 52 months, 66.6% of the GPS 1 are progression-free after 44 months and 76.92% of the GPS 2 after 47 months. These are the results of NRM: 100% of GPS 0 after 52 months, 53.3% of the GPS 1 after 44 months, 35.16 % of the GPS 2 after 47 months. 14.29% of the GPS 0 develop a significant aGvHD within 100 days, 50% of the GPS 1 and 46.15% of the GPS 2 (see Figure 16).

The median survival of the GPS 0 is 24 months, 16 months in the group of GPS 1a, 8.5 months in the GPS 2. This was not measurable for the GPS 1b. The GPS 0 have an OS of 34.57% after 60 months, the GPS 1a 33% after 38 months, the GPS 1b 62.5% after 26 months and the GPS 2 have no more survivors after 48 months. PFS results: 75% of the GPS 0 are progression-free after 60 months, 40% of the GPS 1a after 38 months, 75% of the GPS 1b after 26 months and 83.3% of the GPS 2 after 48 months. These are the results for NRM: 49.38% of the GPS 0 after 60 months, 100% of the GPS 1a after 38 months, 83.3% of the GPS 1b after 26 months and 0% of the GPS 2 after 48 months. 40% of the GPS 0 develop a significant aGvHD within 100 days, 40% of the GPS 1a as well, 50% of the GPS 1b and 75% of the GPS 2 (see Figure 17).

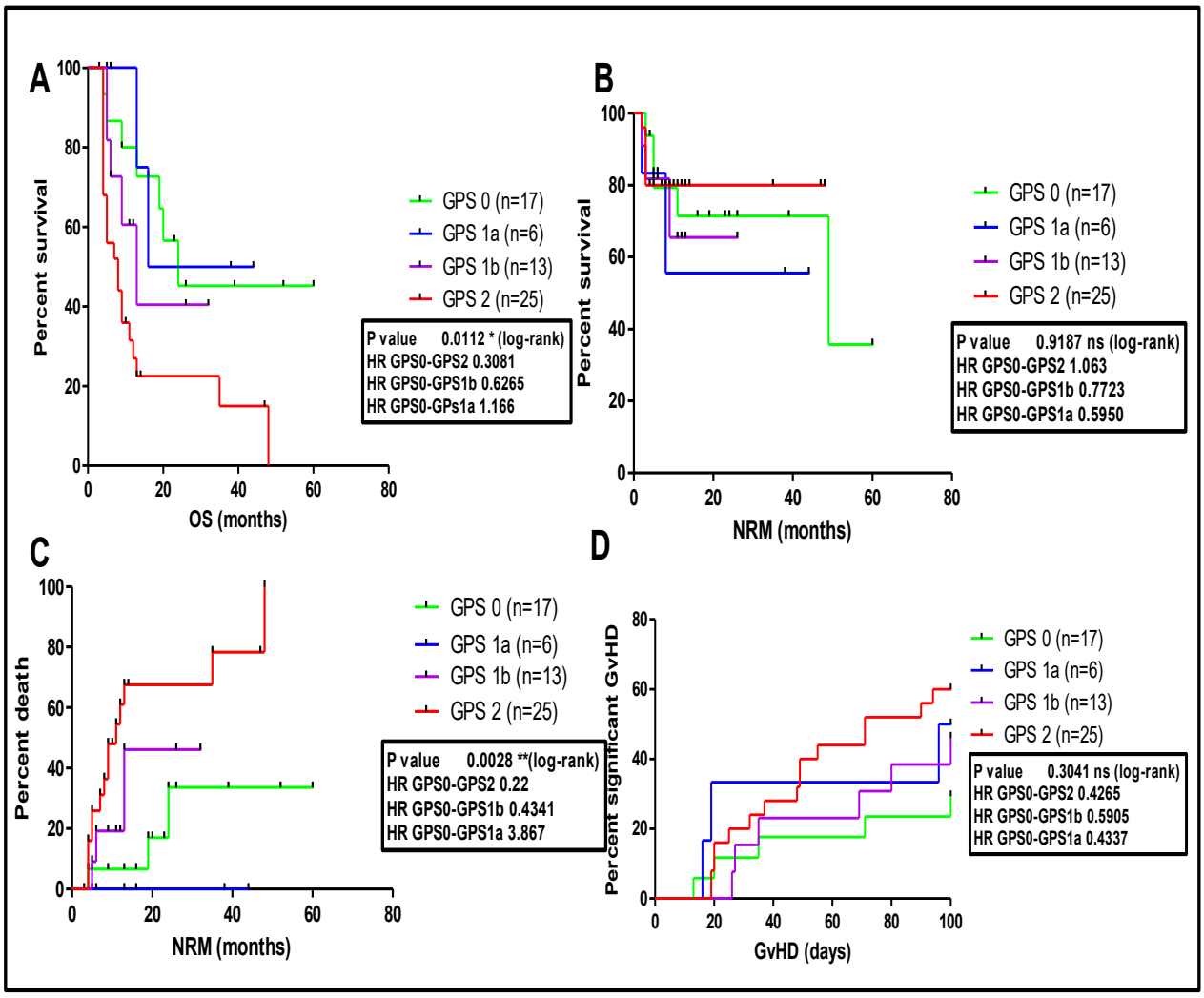


Figure 15: Survival results analysed by "modified GPS" on d+100 with all recipients with RIC, matched HLA, no UW, n=61; A Overall Survival (OS) of 61 patients with RIC, matched HLA, pBSC: according to GPS B Progression Free Survival (PFS) of 61 patients according to GPS; C Non-Relapse Mortality (NRM) of 61 patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 61 patients according to GPS.

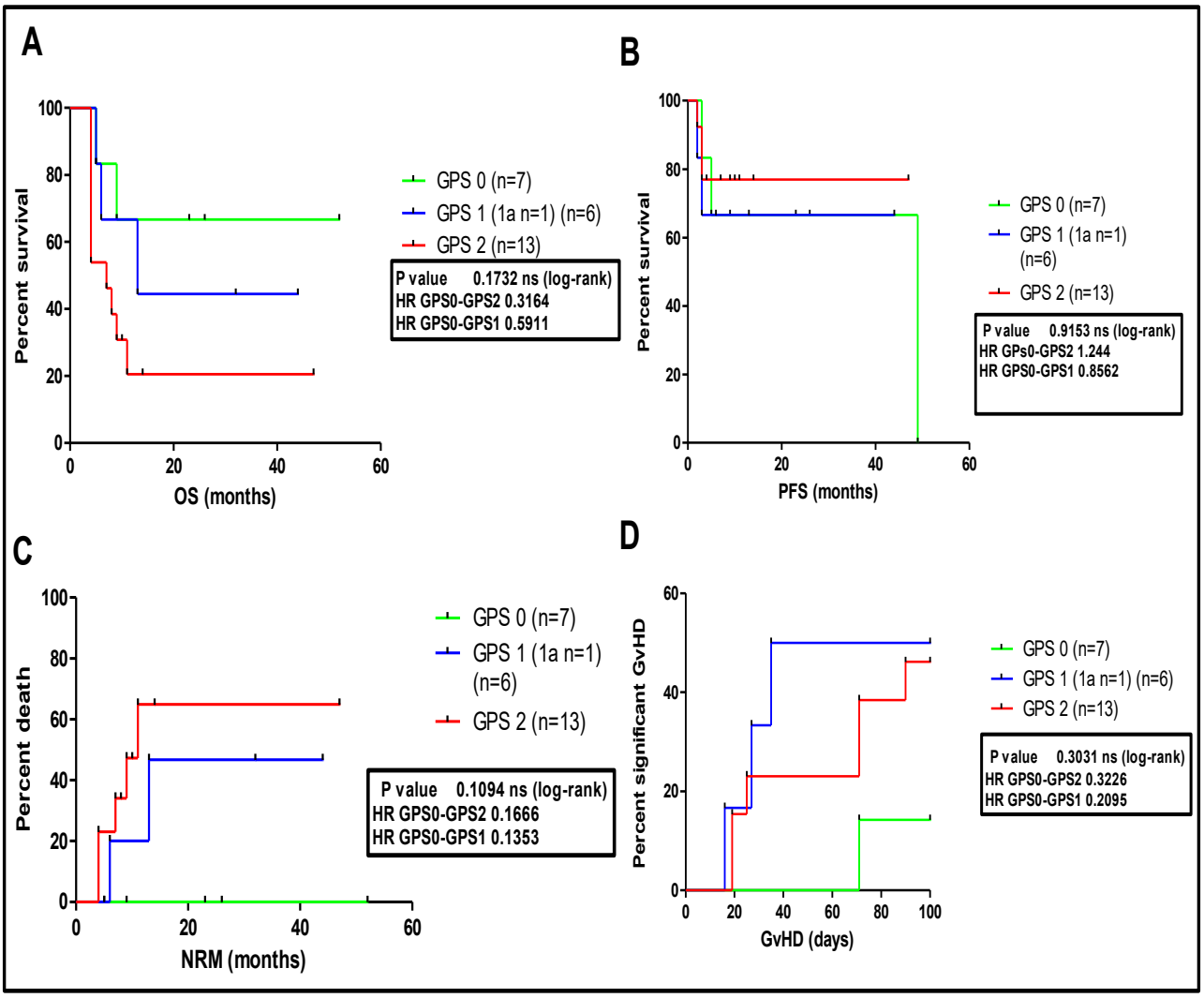


Figure 16: Survival results analysed by "modified GPS" on d+100 with female recipients with RIC, matched HLA, no UW, n=26; A Overall Survival (OS) of 26 female patients with RIC, matched HLA, pBSC: according to GPS B Progression Free Survival (PFS) of 26 female patients according to GPS; C Non-Relapse Mortality (NRM) of 26 female patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 26 female patients according to GPS.

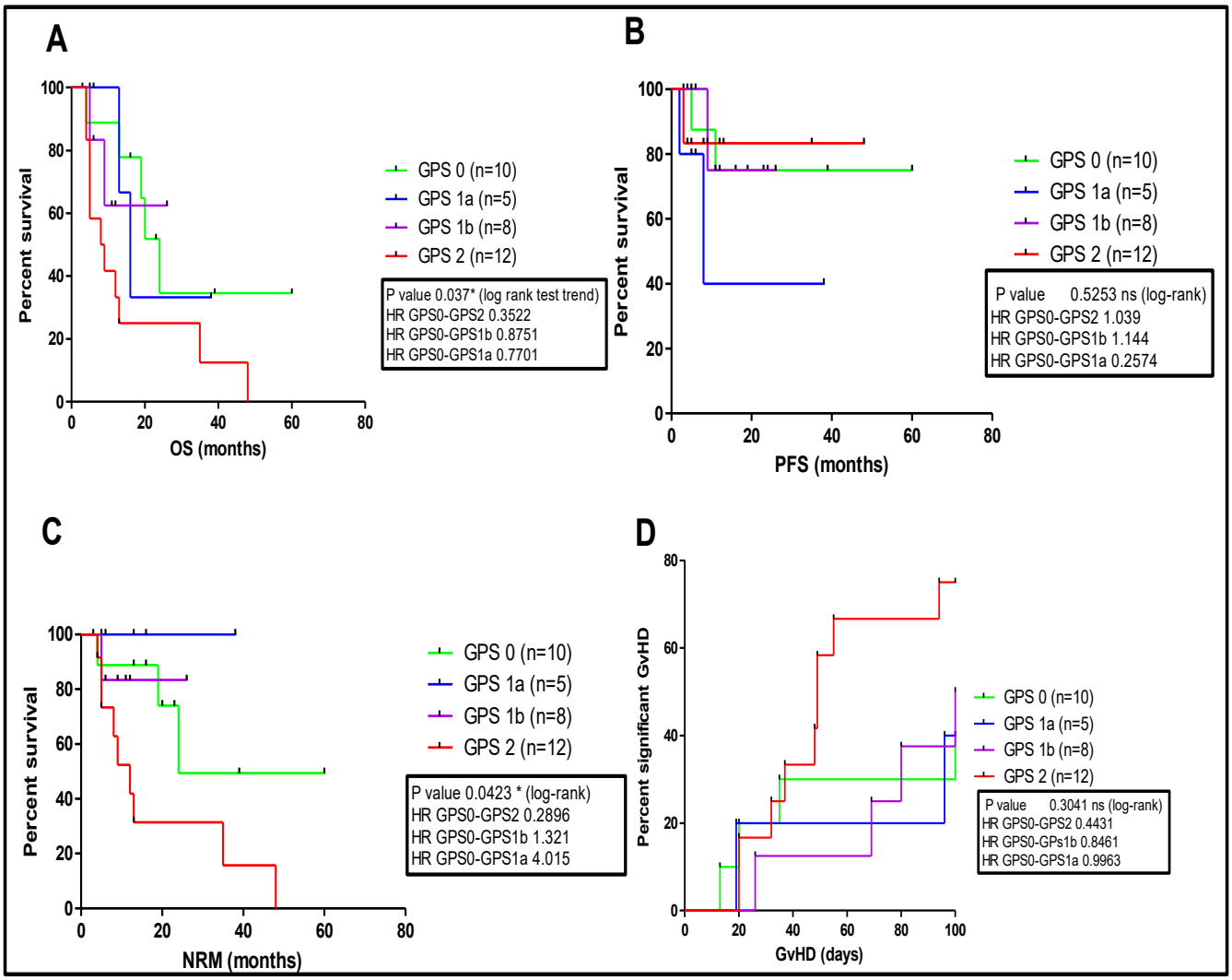


Figure 17: Survival results analysed by "modified GPS" on d+100 with male recipients with RIC, matched HLA, no UW, n=35; A Overall Survival (OS) of 35 male patients with RIC, matched HLA, pBSC: according to GPS B Progression Free Survival (PFS) of 35 male patients according to GPS; C Non-Relapse Mortality (NRM) of 35 male patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 35 male patients according to GPS.

4.5.4 Clinical outcomes according to GPS on d+30

The median survival in the group of GPS 0 is 58 months, the GPS 1 have a median survival of 38 months and the GPS 2 8 months. After 60 months, the OS in the GPS 0 is 48.47%, 44.04% in the GPS 1 and 15.31% in the GPS 2 (after 57 months). The progression-free survival is 50.9% in the GPS 0, 48.7% in the GPS 1 and 57.13% in the GPS 2 (after 57 months). These are the NRM results: 76.92% of the GPS 0 and 64.92% of the GPS 1 after 60 months and 28.6% of the GPS 2 after 57 months. 37.1% of the GPS 0 develop a significant aGvHD within 100 days, 50,66% of the GPS 1 and 46.46% of the GPS 2 (see Figure 18).

In females, the median survival in the GPS 0 is 32 months, in the GPS 1 22 and in the GPS 2 6 months. In the GPS 0, the OS is 42.93% after 60 months, 43.81% in the GPS 1 (60 months) and 20.13% in the GPS 2 after 57 months. In the GPS 0, 44.05% live progression-free after 60 months, 57.28% in the GPS 1 after 60 months and 62.5% in the GPS 2 after 57 months. NRM results: In the GPS 0 there are 76.9% after 60 months, 65.4% in the GPS 1 and 36.44% in the GPS 2 (57 months). Within 100 days, 35.8% of the GPS 0 develop a significant aGvHD, 45.31% of the GPS 1 and 54.34% of the GPS 2 (see Figure 19).

In male, the median survival in the GPS 1 is 45 months and in the GPS 2 11 months. This was not measurable for the GPS 0. In the OS, there are 53.17% of the GPS 0 and 36.31 % of the GPS 1 still alive after 60 months. After 55 months, the OS of the GPS2 is 14.04%. These are the PFS results: 56.75% in the group of GPS 0 ,40.56% in the GPS 1 and 53.17% in the GPS 2 (55 months). NRM: 77.06% in the GPS 0, 65.68% in the GPS 1 and 26.38% in the GPS 2 (55 months). Within 100 days, 37.14% of the GPS 0 develop a significant aGvHD, 54.55% of the GPS 1 and 39.62% of the GPS 2 (see Figure 20).

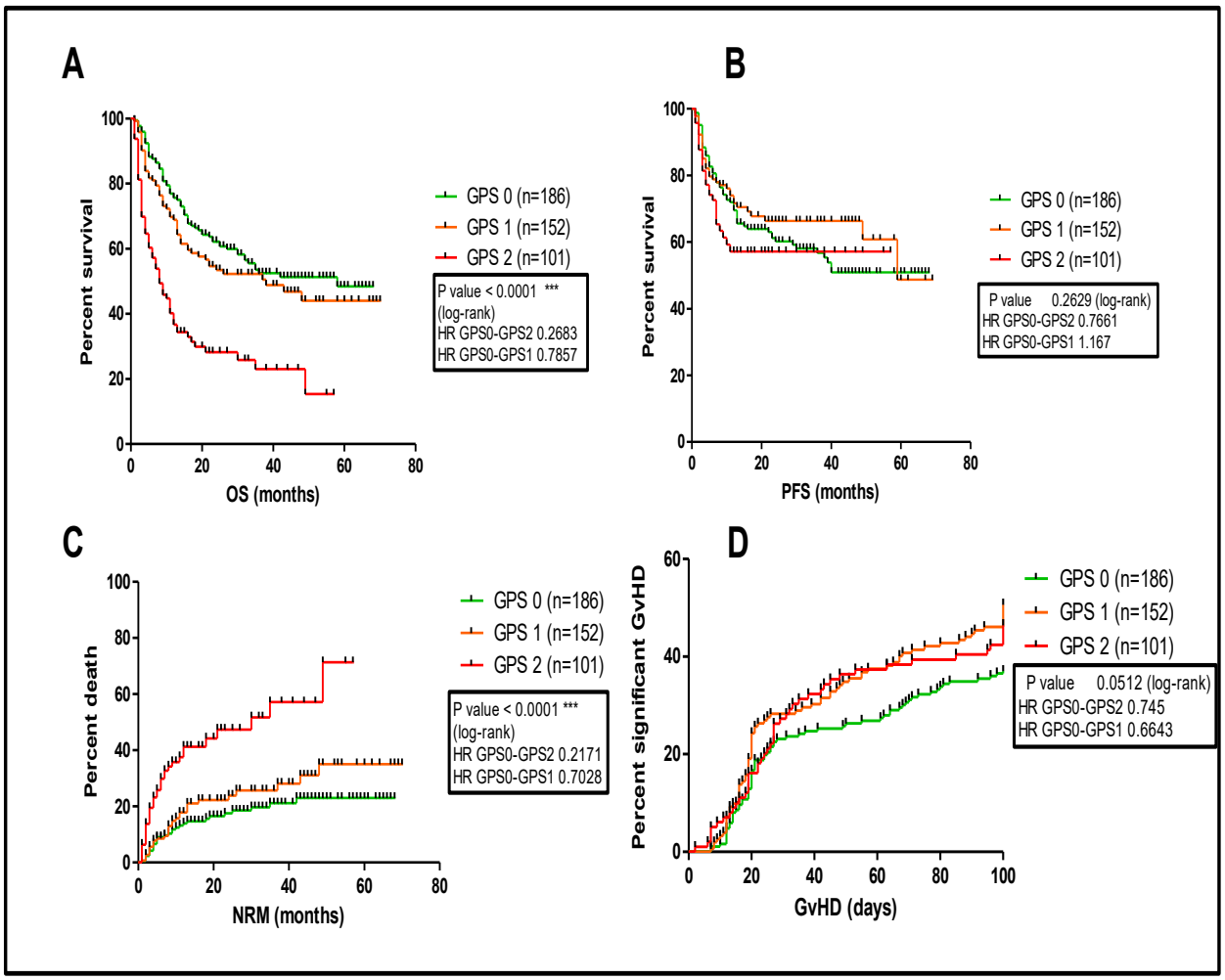


Figure 18: Survival results analysed by "modified GPS" on d+30 with all recipients, no UW, n=439; A Overall Survival (OS) of 439 patients: according to GPS B Progression Free Survival (PFS) of 439 patients according to GPS; C Non-Relapse Mortality (NRM) of 439 patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 439 patients according to GPS

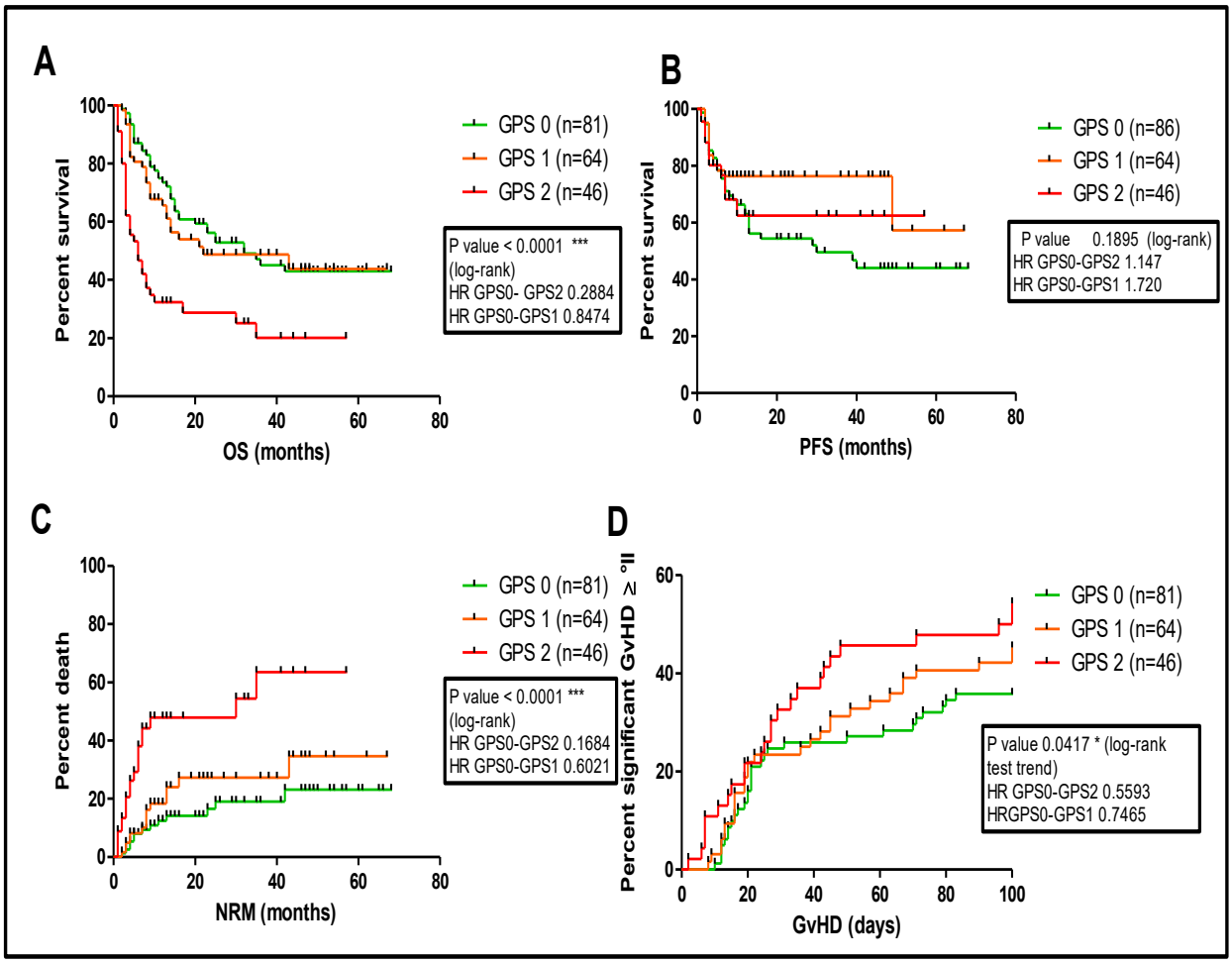


Figure 19: Survival results analysed by "modified GPS" on d+30 with female recipients, no UW, n=191;A Overall Survival (OS) of 191 female patients: according to GPS B Progression Free Survival (PFS) of 191 female patients according to GPS; C Non-Relapse Mortality (NRM) of 191 female patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 191 female patients according to GPS.

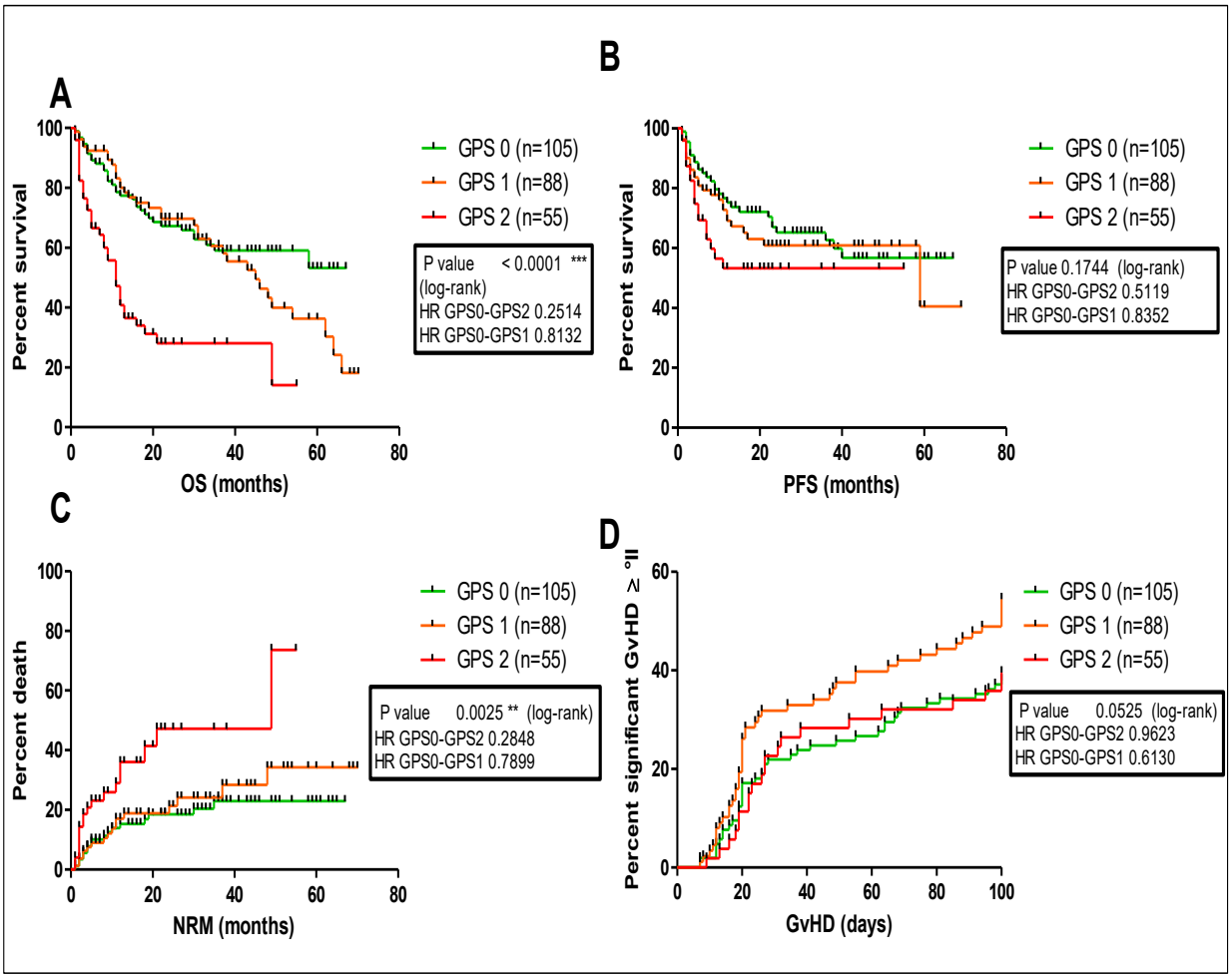


Figure 20: Survival results analysed by "modified GPS" on d+30 with male recipients, no UW, n=248: A Overall Survival (OS) of 248 male patients: according to GPS B Progression Free Survival (PFS) of 248 male patients according to GPS; C Non-Relapse Mortality (NRM) of 248 male patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 248 male patients according to GPS.

4.5.5 Clinical outcomes according to GPS on d+30, subgroup analysis with RIC, 10/10 HLA and pBSC

In the GPS 0, the median survival is 36 months and 11.5 months in the GPS 2. This was not measurable for the GPS 1. After 60 months, the OS in the GPS 0 is 43.2%, 51.22% in the GPS 1 and 38% in the GPS 2 (57 months). A progression-free survival have 52.89% in the GPS 0 and 40.82% of the GPS 1 (after 60 months), 54.33 of the GPS 2 after 57 months. These are the results of the NRM: 73.77% of the GPS 0 and 68.59% of the GPS 1 after 60 months, 68.59% of the GPS 2 after 57 months. Within 100 days, 37.5% of the GPS 0 develop a significant aGvHD, the groups GPS 1 and GPS 2 each develop 47% (see Figure 21).

In females, the median survival in the group GPS 0 is 35 months and in the GPS 2 8 months. This was not measurable for GPS 1. The OS after 60 months is 40.51% in the GPS 0, 55.2% in

the GPS 1 after 54 months and 37.19% in the GPS 2 after 57 months. A progression-free life had 47.28% of the GPS 0 after 60 months, 40.58% of the GPS 1 after 54 months and 60.45% of the GPS 2 after 57 months. These are the results for the NRM: 75.06% in the GPS 0 (60 months), 74.22% in the GPS 1 after 54 months and 64.8% in the GPS 2 after 57 months. The GPS 0 and GPS 1 develop each 41.18% significant aGvHD within 100 days, the group GPS 2 63.63% (see Figure 22).

In males, the median survival in GPS 0 is 58 months and in the GPS 2 12 months. This was not measurable for the GPS 1. The OS in the GPS 0 is 45.63% and 51.42% in the GPS 1 after 60 months. In the GPS 2, 39% still live after 55 months. The GPS 0 have a progression-free survival of 57% after 60 months, GPS 1 44.6% and GPS 2 50.31% after 55 months. These are the results of the NRM: 72.66% in the GPS 0, 64.16% in the GPS 1 and 70.05% in the GPS 2 (55 months). 37.88% of the GPS 0 develop a significant aGvHD within 100 days, 51% of the GPS 1 and 33.3% of the GPS 2 (see Figure 23).

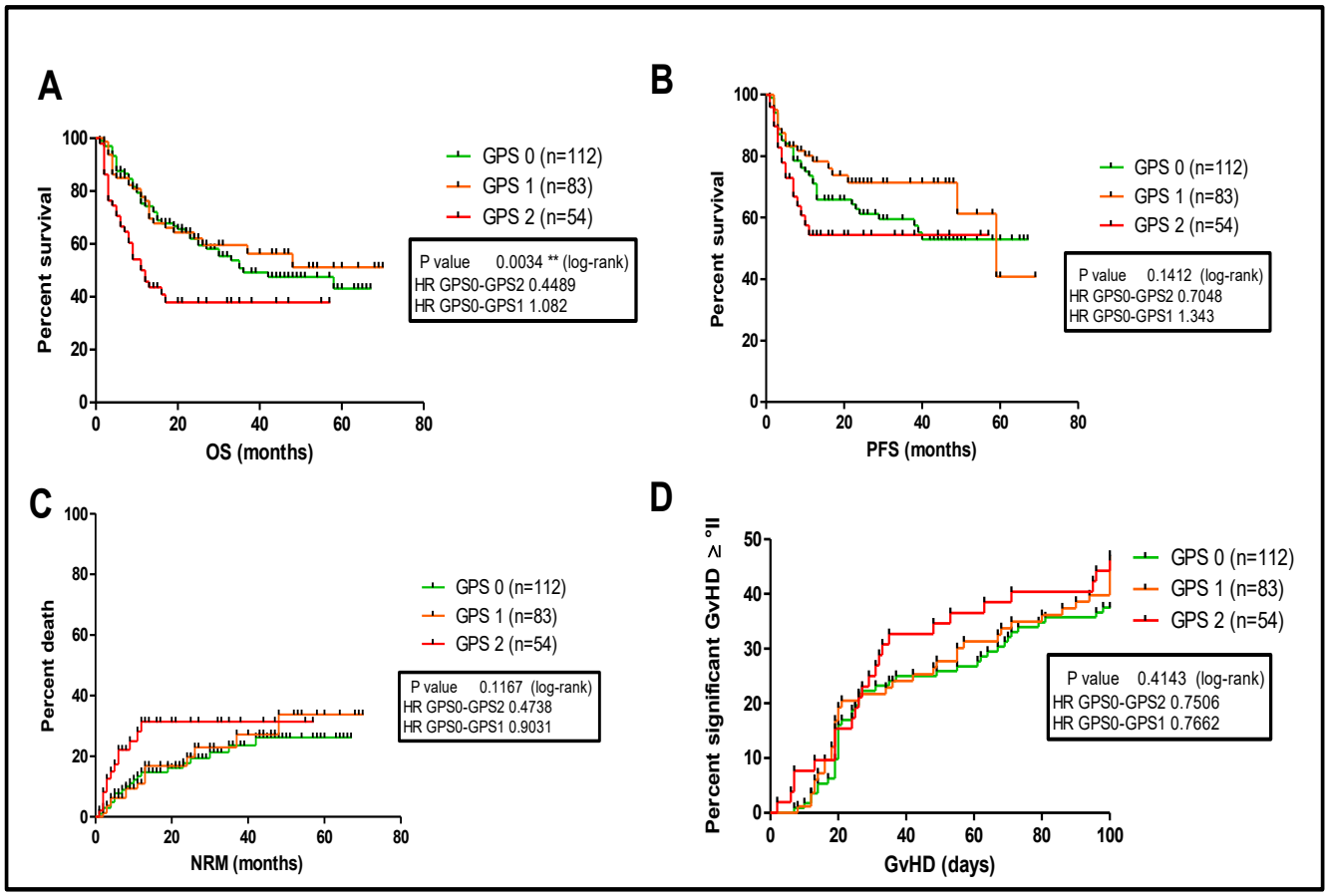


Figure 21: Survival results analysed by "original GPS" on d+30 with all recipients with RIC, no UW, n=249 A Overall Survival (OS) of 249 patients, RIC, matched HLA and pBSC: according to GPS B Progression Free Survival (PFS) of 249 patients according to GPS; C Non-Relapse Mortality (NRM) of 249 patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 249 patients according to GPS.

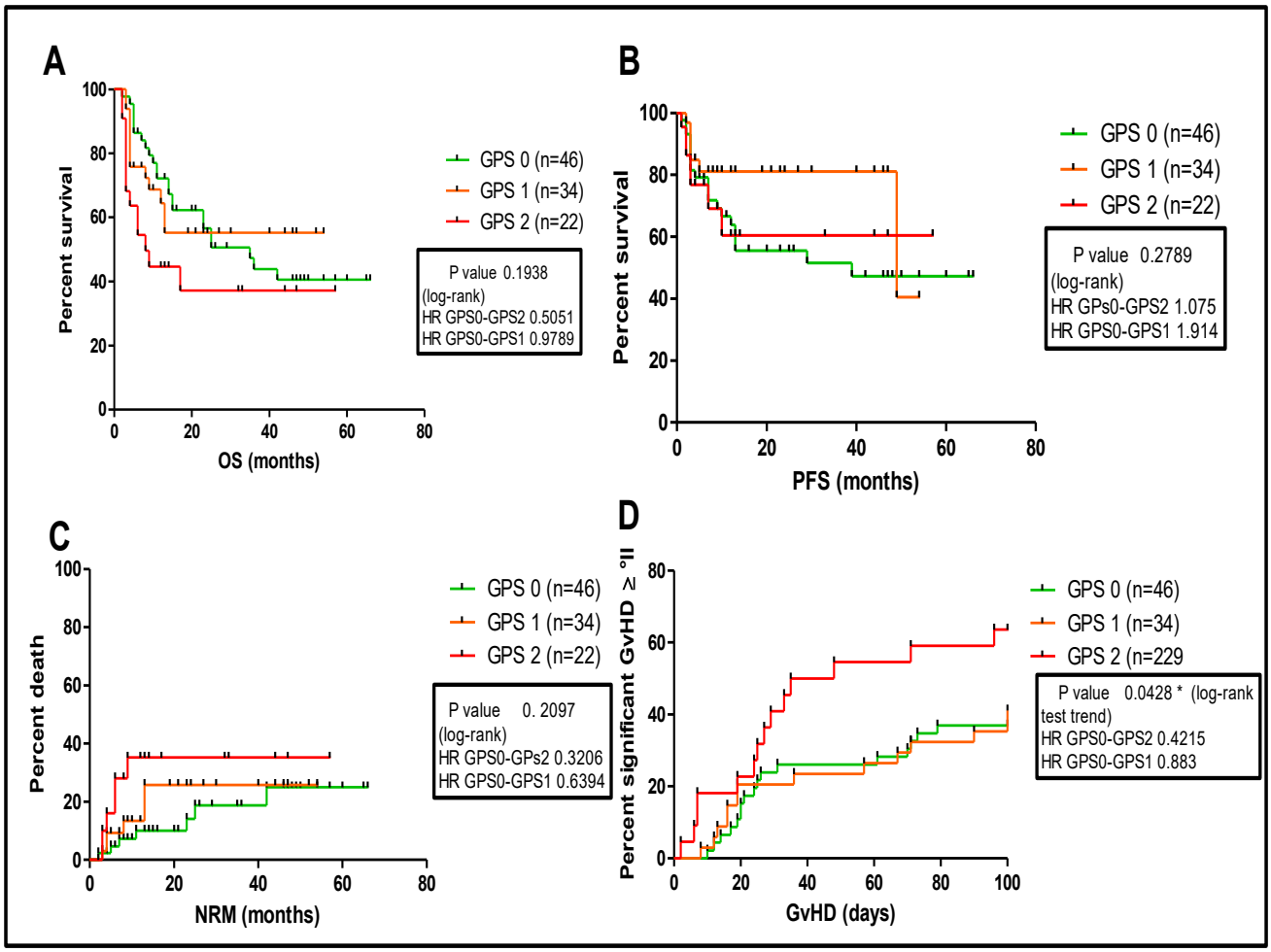


Figure 22: Survival results analysed by "original GPS" on d+30 with female recipients with RIC, no UW, n=102: A Overall Survival (OS) of 102 female patients: according to GPS B Progression Free Survival (PFS) of 102 female patients according to GPS; C Non-Relapse Mortality (NRM) of 102 female patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 102 female patients according to GPS

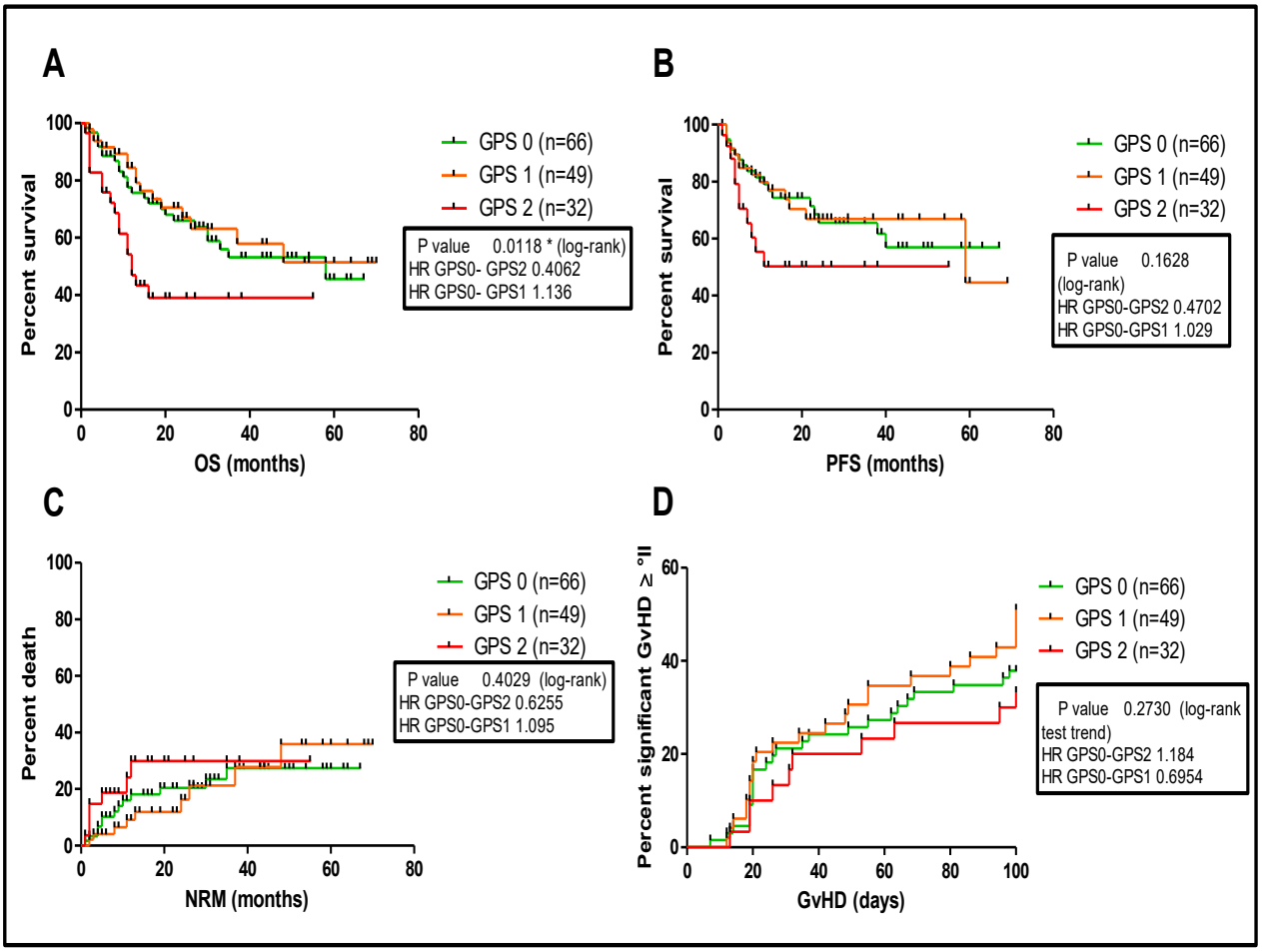


Figure 23: Survival results analysed by "original GPS" on d+30 with male recipients with RIC, no UW, n=147: A Overall Survival (OS) of 147 male patients: according to GPS B Progression Free Survival (PFS) of 147 male patients according to GPS; C Non-Relapse Mortality (NRM) of 147 male patients according to GPS; D acute Graft-versus-Host-disease (aGvHD) of 147 male patients according to GPS

4.6 Neutrophil- to- Lymphocyte Ratio (NLR)

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, respectively (Yodying et al. 2016). The cut-off values were determined by frequency distribution and X-Y correlations: details can be found in the following figures.

4.6.1 Cut-off Tests

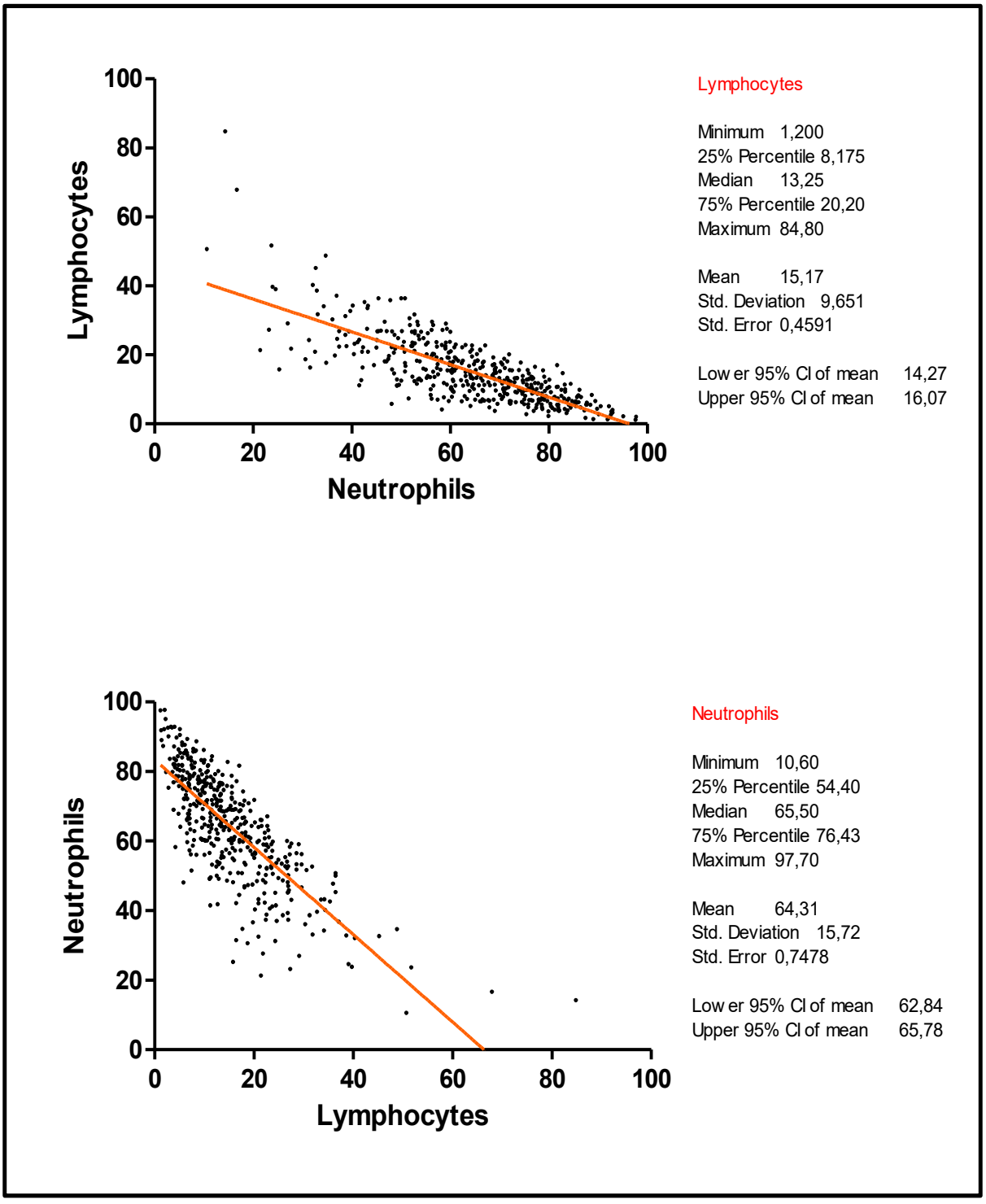
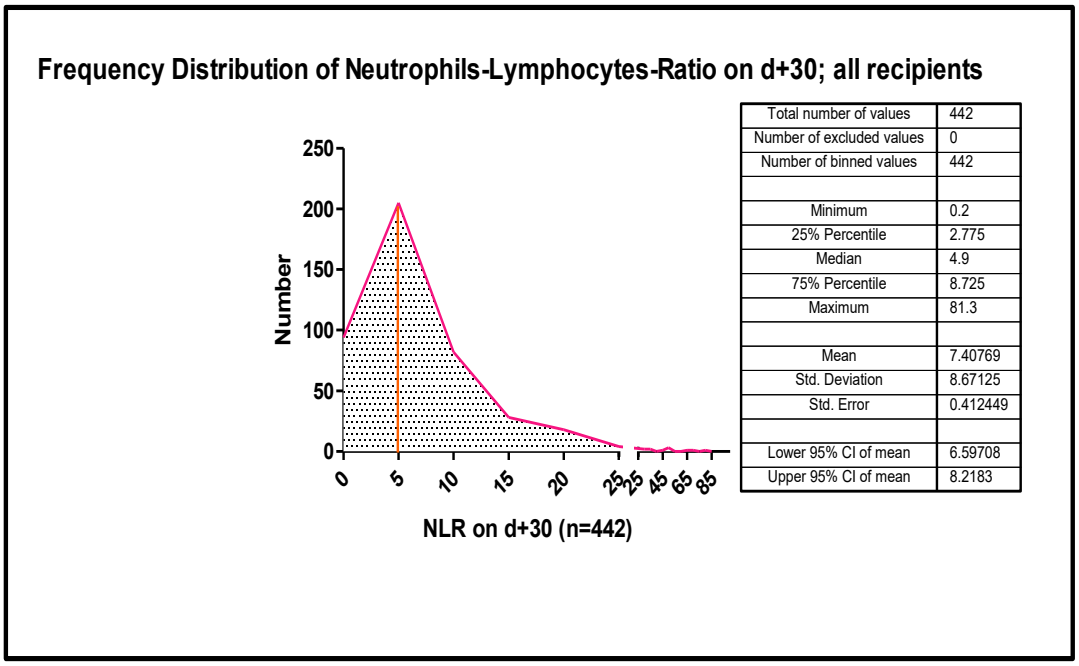


Figure 24: XY-Correlation of Lymphocytes and Neutrophils on d+30



Total number of values	442
Number of excluded values	0
Number of binned values	442
Minimum	0.2
25% Percentile	2.775
Median	4.9
75% Percentile	8.725
Maximum	81.3
Mean	7.40769
Std. Deviation	8.67125
Std. Error	0.412449
Lower 95% CI of mean	6.59708
Upper 95% CI of mean	8.2183

Figure 25: Histogram of Frequency distribution of NLR on d+30, all recipients

4.6.2 Cut-off Values for NLR on d+100

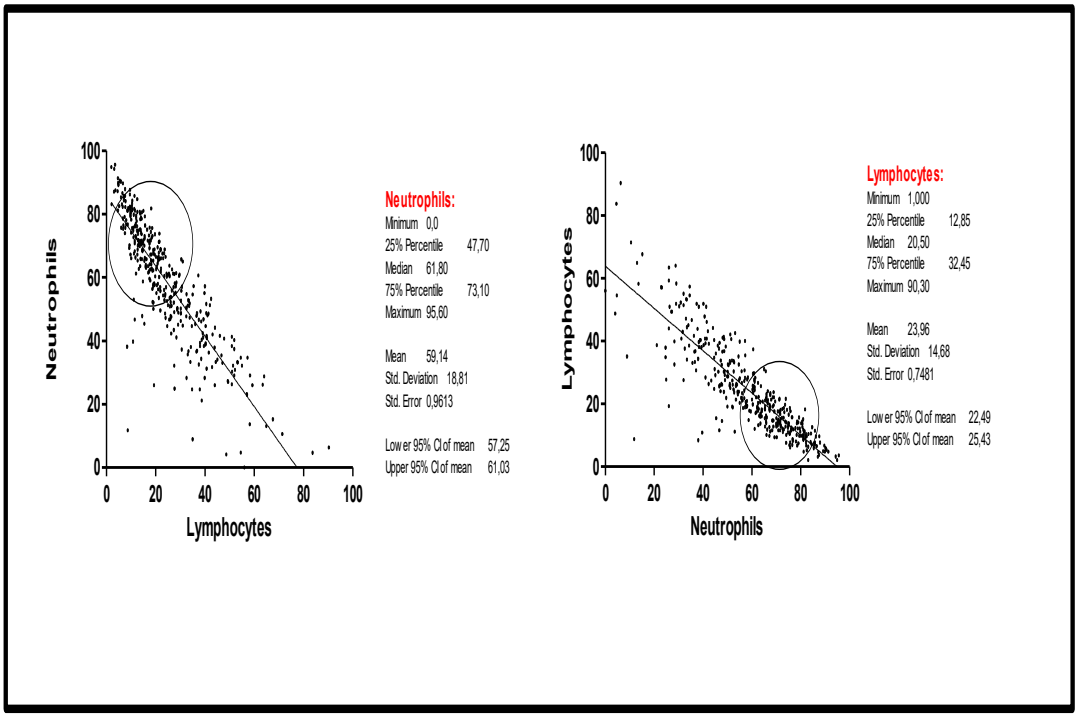


Figure 26: XY-Correlation of Lymphocytes and neutrophils on d+100

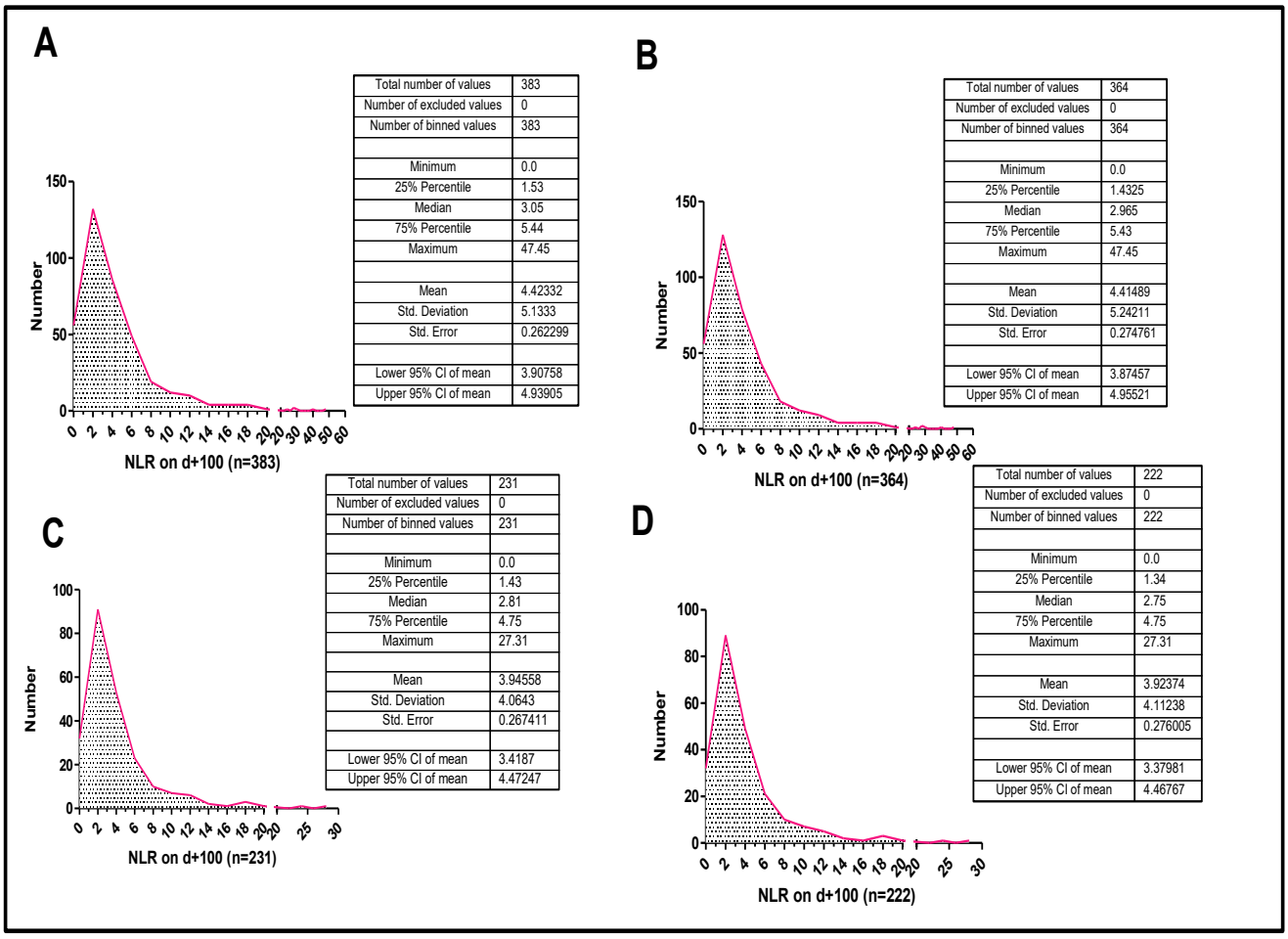


Figure 27: Histograms of Frequency distribution of NLR on d+100; Histograms of frequency distribution on d+100 for NLR, median ~3; A: all recipients, B: all recipients without UW, C: All recipients with RIC and 10/10 HLA and pbsc, D: All recipients with RIC and 10/10 HLA and pbsc without UW

4.7 Immuno-Metabolic-Score (IMS)

Immuno-Metabolic-Score	Protein mg/l	C-reactive Protein mg/L	NLR
IMS 0	≥64	≤10	≤2
IMS 1a	<64	≤10	≤2
IMS 1b	≥64	>10	≤2
IMS 1c	≥64	≤10	>2
IMS 2a	<64	≤10	>2
IMS 2b	≥64	>10	>2
IMS 2c	<64	>10	≤2
IMS 3	<64	>10	>2

Table 11: Immunometabolic Score (IMS) and corresponding Protein, C-Reactive Protein and NLR

4.7.1 Clinical outcomes according to IMS on d+30 with NLR 2, all recipients

The median survival in the IMS 2 is 23 months and in the IMS 3 7 months. This was not measurable for the groups IMS 0 and 1. The OS in the IMS 0 is 58.03% after 60 months, 50.38% in the IMS 1, 38.22% in the IMS 2 and 17.35% in the IMS 3 after 49 months. The PFS after 60 months in the IMS 0 is 62.63%, 46.18% in the IMS 1, 58.39% in the IMS 2 and 54.44% in the IMS 3 after 49 months. These are the NRM results: 77.78% in the IMS 0, 80.67% in the IMS 1, 60.59% in the IMS 2 and 32.47% in the IMS 3 after 59 months. Within 100 days, 23.08% of the IMS 0 develop a significant aGvHD, 36.84% of the IMS 1, 50.84% of the IMS 2 and 48.68% of the IMS 3 (see Figure 28).

In females, the median survival in the IMS 0 was not measurable, 32 months in the IMS 1, 23 months in the IMS 2 and 5 months in the IMS 3. The OS in the IMS 0 is 75% after 60 months, 39.7% in the IMS 1, 41.37% in the IMS 2 and 8.48% in the IMS 3 after 47 months. The PFS in the IMS 0 is 62.2% after 46 months, 44.16% in the IMS 1 and 58.3% in the IMS 2 after 60 months, 62.75% in the IMS 3 after 47 months. These are the NRM results: in the IMS 0 100% after 60 months, 74.71% in the IMS 1, 66.91% in the IMS 2 and 17.62% in the IMS 3. Within 100 days, 20% of the IMS 0 develop a significant aGvHD, 35.94% of the IMS 1, 45.98% of the IMS 2 and 55.88% of the IMS 3 (Figure 29).

In males, the median survival in the IMS 0 is 37 months, in the IMS 2 22 months and in the IMS 3 11 months. This was not measurable for the IMS 1. The OS after 60 months in the IMS 0 is 48.21%, in the IMS 1 59.68%, 35.85% in the IMS 2 and 28.24% in the IMS 3 after 49 months. The PFS in the IMS 0 is 64.65%, 47.65% in the IMS 1, 58.85% in the IMS 2 and 48.14% in the IMS 3 after 49 months. These are the NRM results: 67.5% in the IMS 0, 85.14% in the IMS 1, 56.08% in the IMS 2, 51.09% in the IMS 3. Within 100 days, 25% of the IMS 0 develop a significant aGvHD, 37.5% of the IMS 1, 53.92% of the IMS 2 and 42.86% of the IMS 3 (see Figure 30).

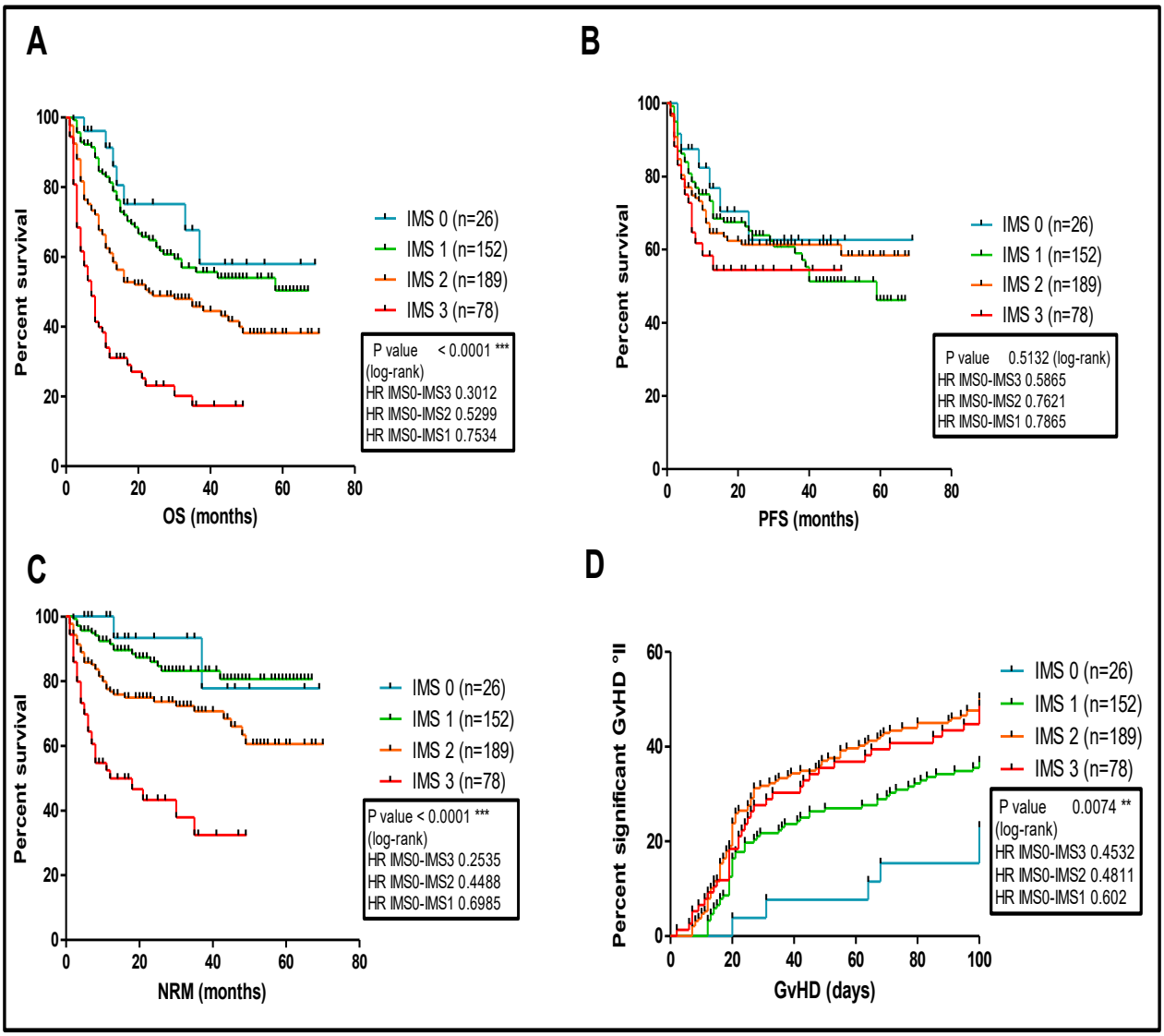


Figure 28: Survival results analysed by IMS on d+30: all recipients, no UW, n= 445;: A Overall Survival (OS) of 445 recipients : according to IMS B Progression Free Survival (PFS) of 445 patients: according to IMS C Non-Relapse Mortality (NRM) of 445 patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 445 patients: according to IMS

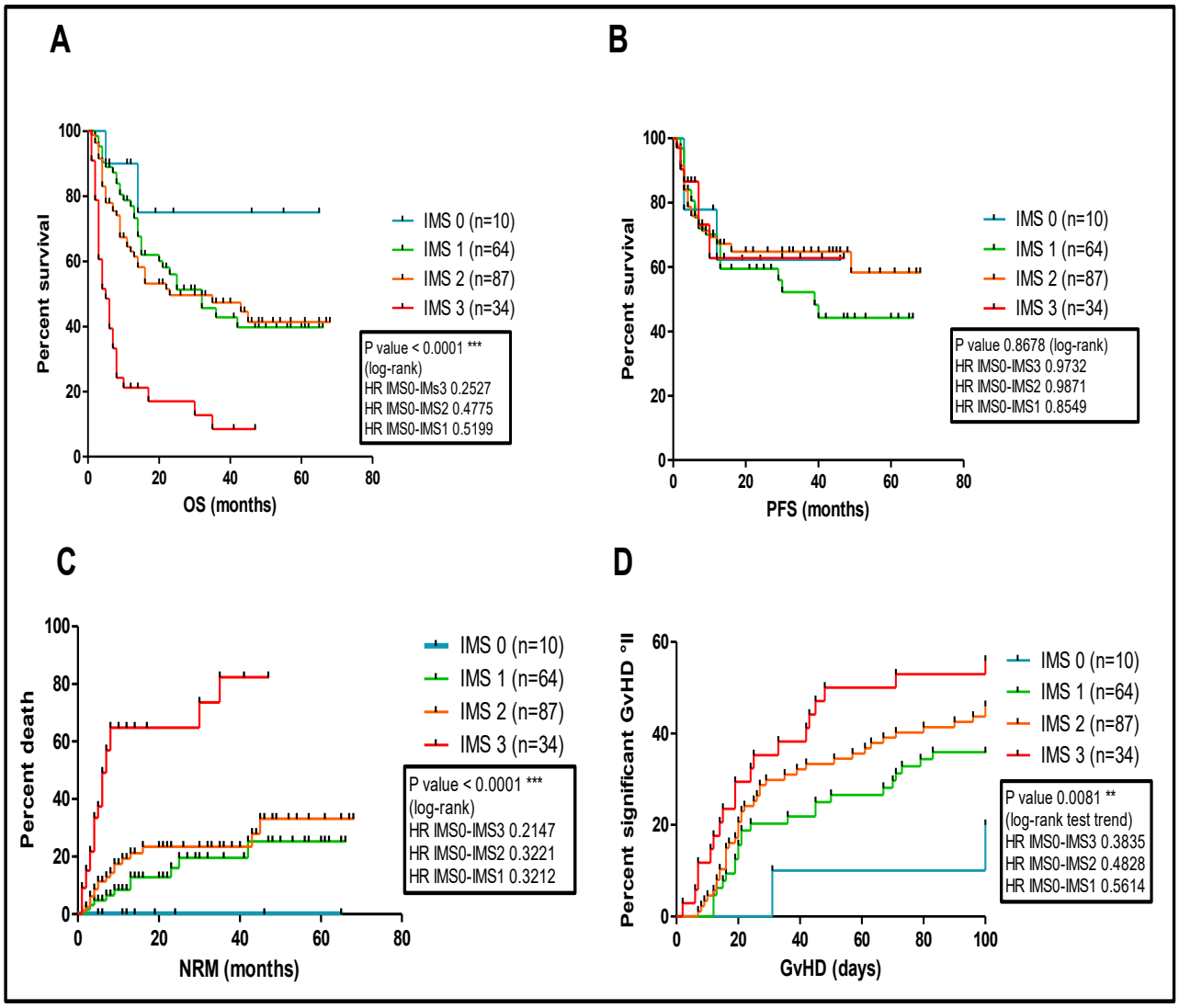


Figure 29: Survival results analysed by IMS on d+30: female recipients, no UW, n= 195;: A Overall Survival (OS) of 195 female recipients: according to IMS B Progression Free Survival (PFS) of 195 female patients: according to IMS C Non-Relapse Mortality (NRM) of 195 female patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 195 female patients: according to IMS

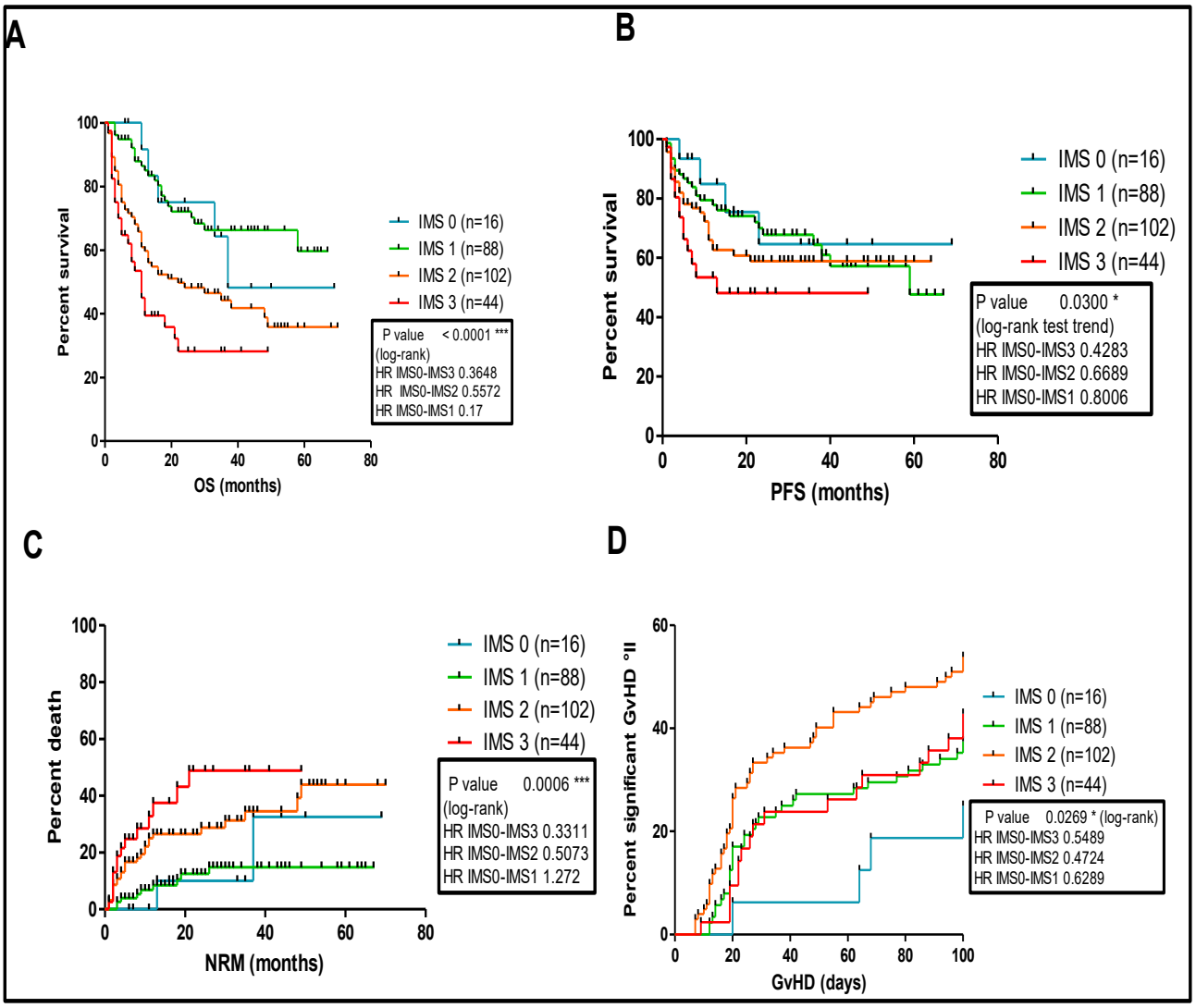


Figure 30: Survival results analysed by IMS on d+30: male recipients, no UW, n= 250; A Overall Survival (OS) of 250 male recipients : according to IMS B Progression Free Survival (PFS) of 250 male patients: according to IMS C Non-Relapse Mortality (NRM) of 250 male patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 250 male patients: according to IMS

4.7.2 Clinical outcomes according to IMS on d+30 with NLR 2: subgroup analysis with RIC, 10/10 HLA and pBSC without UW

The median survival in the IMS 1 is 58 months, 35 months in the IMS 2 and 8 months in the IMS 3. This was not measurable for the IMS 0. The OS in the IMS 0 is 53.28% after 60 months, 47.49% in the IMS 1, 43.35% in the IMS 2 and 28.46% in the IMS 3 (47 months). The PFS after 60 months is 63.99% in the IMS 0, in the IMS 1 44.94%, in the IMS 2 60.32% and in the IMS 3 44.39% (47 months). These are the NRM results after 60 months: 76.39% in the IMS 0, 79.69% in the IMS 1, 61.23% in the IMS 2 and 62.63% in the IMS 3 (47 months). Within 100 days, 16.6%

of the IMS 0 develop a significant aGvHD, 33.3% of the IMS 1, 52.9% of the IMS 2 and 48.57% of the IMS 3 (see Figure 31).

The median survival in the IMS 1 is 25 months, 45 months in the IMS 2 and 5 months in the IMS 3. The OS in the IMS 0 is 70% after 60 months, 39.55% in the IMS 1, 44.43% in the IMS 2 and 14.29% in the IMS 3 (47 months). The PFS in the IMS 0 is 60% after 46 months, 52.53% in the IMS 1 after 60 months, 54.29% in the IMS 2 after 57 months and 46.75% in the IMS 3 after 47 months. These are the NRM results: 100% of the IMS 0, 72.12% in the IMS 1, 66.15% in the IMS 2 after 57 months, 50.93% in the IMS 3 after 47 months. Within 100 days, 25% of the IMS 0 develop a significant aGvHD, 31.58% of the IMS 1, 50% of the IMS 2 and 64.29% of the IMS 3 (see Figure 32).

The median survival in the IMS 0 is 37 months, 35 months in the IMS 2 and 11 months in the IMS 3. This was not measurable for the IMS 1. The OS in the IMS 0 is 46.6% after 60 months, 54.21% in the IMS 1, 43.21% in the IMS 2 and 37.69% in the IMS 3 (after 35 months). The PFS after 60 months in the IMS 0 is 70%, 36.52% in the IMS 1, 64.89% in the IMS 2 and 42.16% in the IMS 3 (after 35 months). These are the NRM results: 64.29% in the IMS 0, 84.84% in the IMS 1, 57.98% in the IMS 2 and 68.06% in the IMS 3 after 35 months. 10% of the IMS 0 develop a significant aGvHD within 100 days, 34.48% of the IMS 1, 55.36% of the IMS 2 and 38.09% of the IMS 3 (see Figure 33).

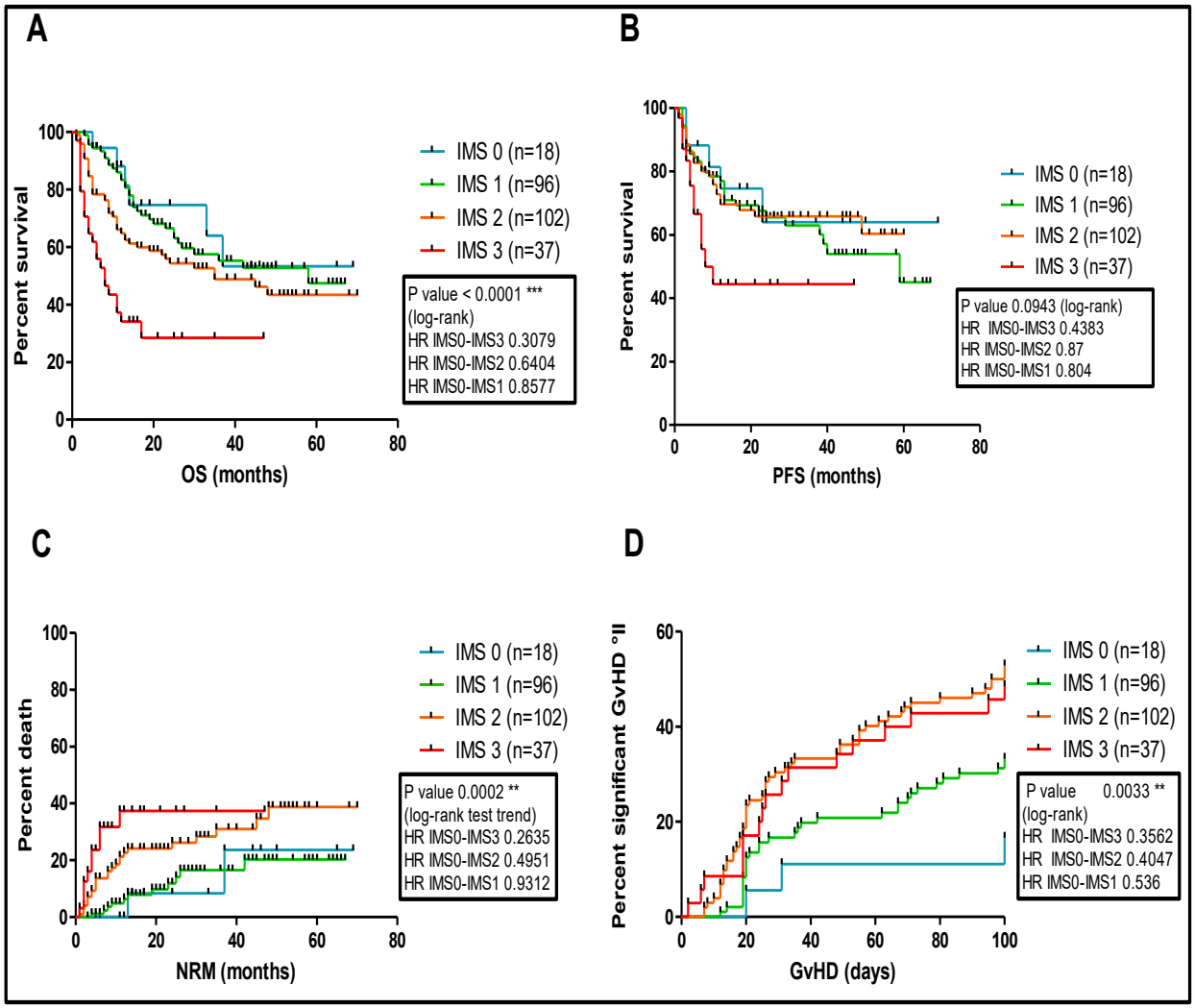


Figure 31 Survival results analysed by IMS on d+30: all recipients, RIC and matched HLA, no UW, n= 253;: A Overall Survival (OS) of 253 recipients with RIC and matched HLA : according to IMS B Progression Free Survival (PFS) of 253 patients: according to IMS C Non-Relapse Mortality (NRM) of 253 patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 253 patients: according to IMS

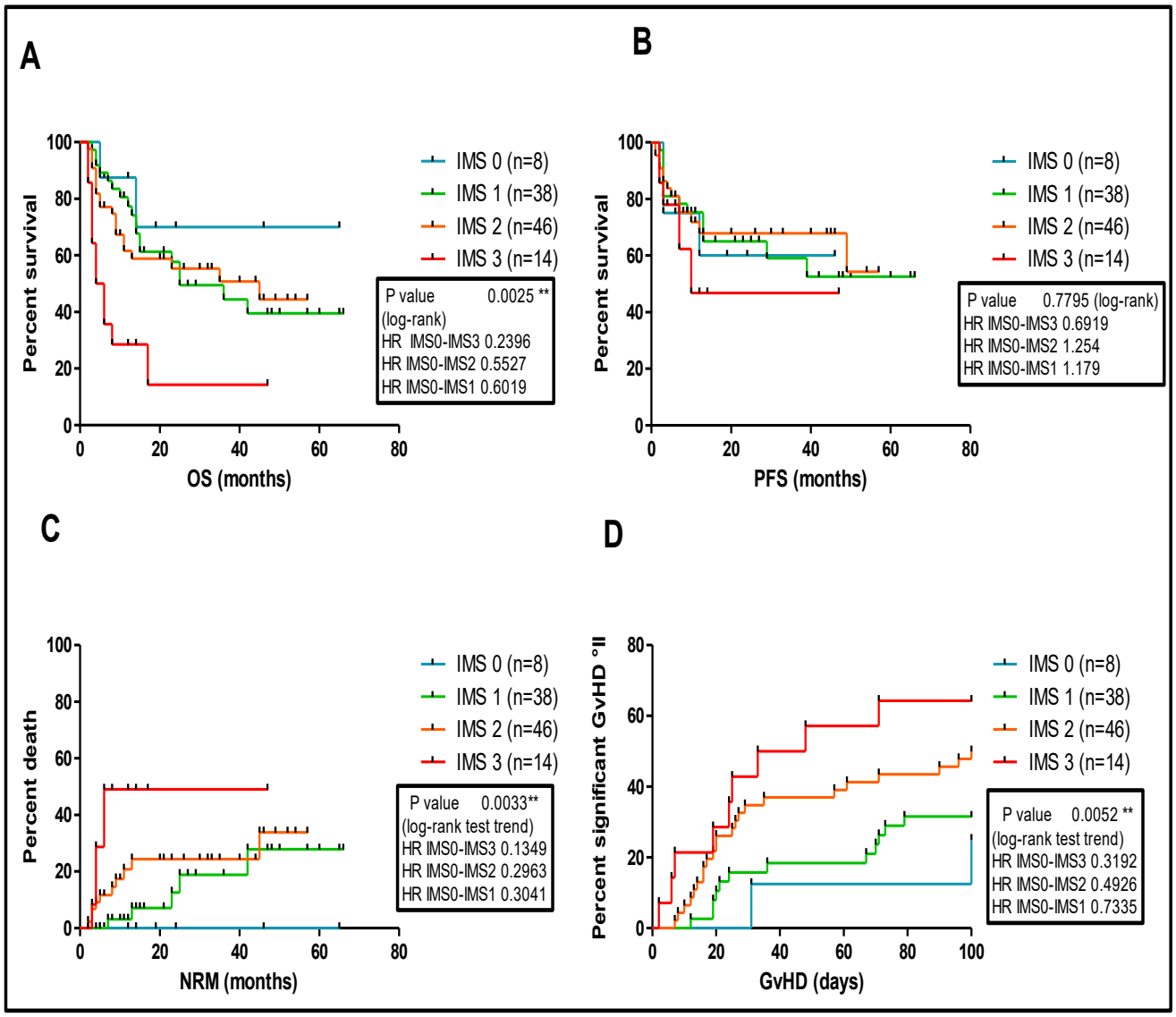


Figure 32: Survival results analysed by IMS on d+30: female recipients, RIC and matched HLA, no UW, n= 106;: A Overall Survival (OS) of 106 female recipients with RIC and matched HLA: according to IMS B Progression Free Survival (PFS) of 106 female patients: according to IMS C Non-Relapse Mortality (NRM) of 106 female patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 106 female patients: according to IMS

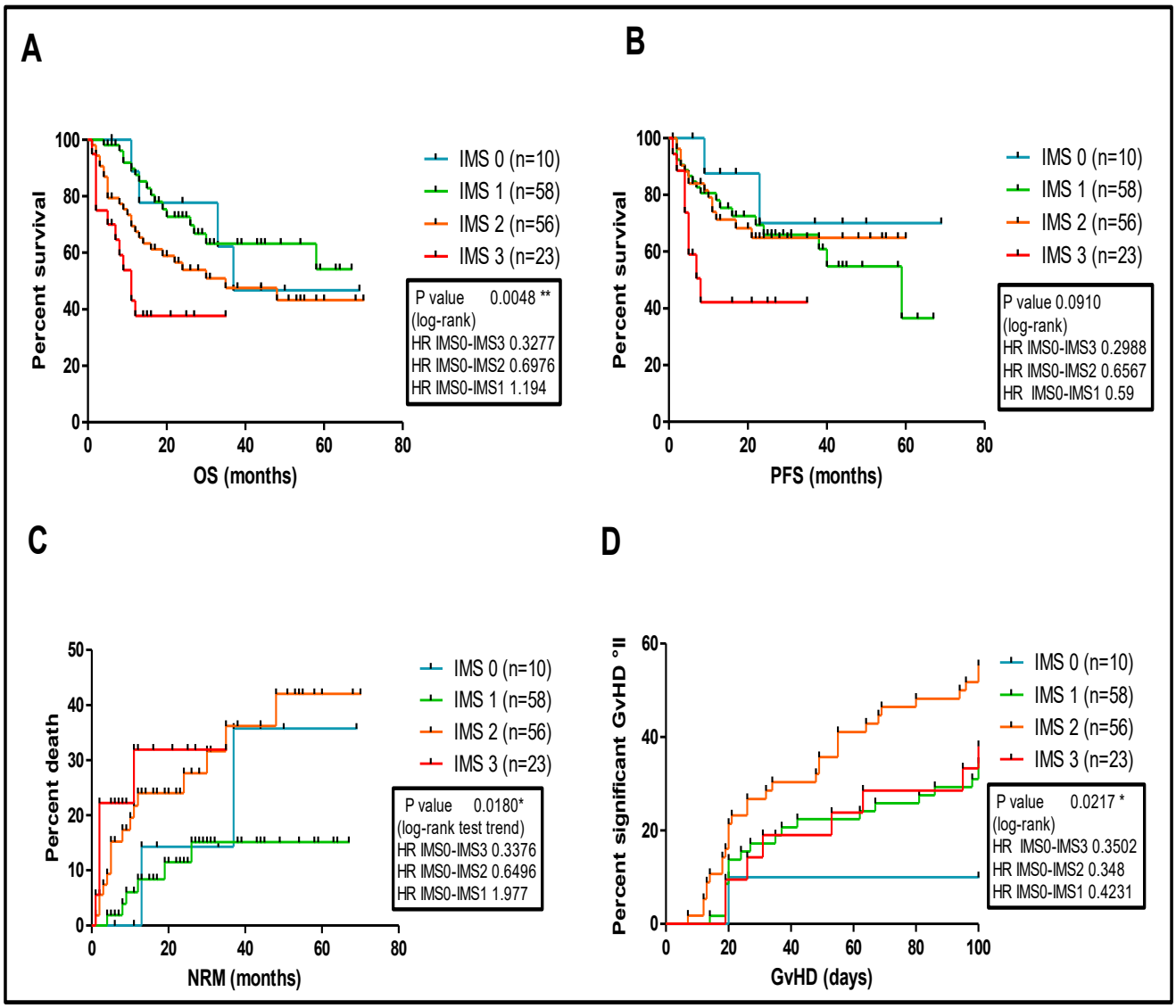


Figure 33: Survival results analysed by IMS on d+30: male recipients, RIC and matched HLA, no UW, n= 147: A Overall Survival (OS) of 147 male recipients with RIC and matched HLA : according to IMS B Progression Free Survival (PFS) of 147 male patients: according to IMS C Non-Relapse Mortality (NRM) of 147 male patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 147 male patients: according to IMS

4.7.3 Clinical outcomes according to IMS on d+100 with NLR 2, all recipients, no UW

The median survival in the IMS 1 is 58 months, 48 months in the IMS 2 and 8 months in the IMS 3. This was not measurable for the IMS 0. The OS in the IMS 0 is 62.87% after 60 months, 45.64% in the IMS 1, 47.7% in the IMS 2 and 19.3% in the IMS 3 after 58 months. The PFS is 35.69% in the IMS 0 after 60 months, 49.2% in the IMS 1, 71.15% in the IMS 2 and 63.79% in the IMS 3 after 58 months. These are the NRM results: 93.82% in the IMS 0, 78.96% in the IMS 1, 60.74% in the IMS 2 and 33.9% in the IMS 3 (after 58 months). Within 100 days, 32.43% of

the IMS 0 develop a significant aGvHD, 32.87% of the IMS 1, 53.7% of the IMS 2 and 64.29% of the IMS 3 (see Figure 34).

In females, the median survival in the IMS 1 is 47 months and 7 months in the IMS 3. This was not measurable for the IMS 0 and 2. The OS after 60 months in the IMS 0 is 50.58%, 42.36% in the IMS 1, 54.39% in the IMS 2 and 17.6% in the IMS 3 (47 months). The PFS in the IMS 0 is 48.47% after 60 months, 44.26% in the IMS 1, 73.79% in the IMS 2 and 60% in the IMS 3 (47 months). These are the NRM results: 85.56% in the IMS 0, 75.83% in the IMS 1, 68.11% in the IMS 2 and 34.74% in the IMS 3 (47 months). Within 100 days, 28.13% of the IMS 0 develop a significant aGvHD, 35.48% of the IMS 1, 50% of the IMS 2 and 55% of the IMS 3 (see Figure 35).

In males, the median survival in the IMS 1 is 58 months, 48 months in the IMS 2 and 8 months in the IMS 3. The OS in the IMS 0 is 72.85% after 60 months, 48.6% in the IMS 1, 42.03% in the IMS 2 and 20.77% in the IMS 3 (after 58 months). The PFS in the IMS 0 is 38.65%, 52.81% in the IMS 1, 69.29% in the IMS 2 and 64.39% in the IMS 3. These are the NRM results: 100% in the IMS 0, 82.48% in the IMS 1, 53.94% in the IMS 2, 33.66% in the IMS 3 after 58 months. Within 100 days, 30.23% of the IMS 0 develop a significant aGvHD, 36.58% of the IMS 1, 54.84% of the IMS 2 and 72.72% of the IMS 3 (see Figure 36).

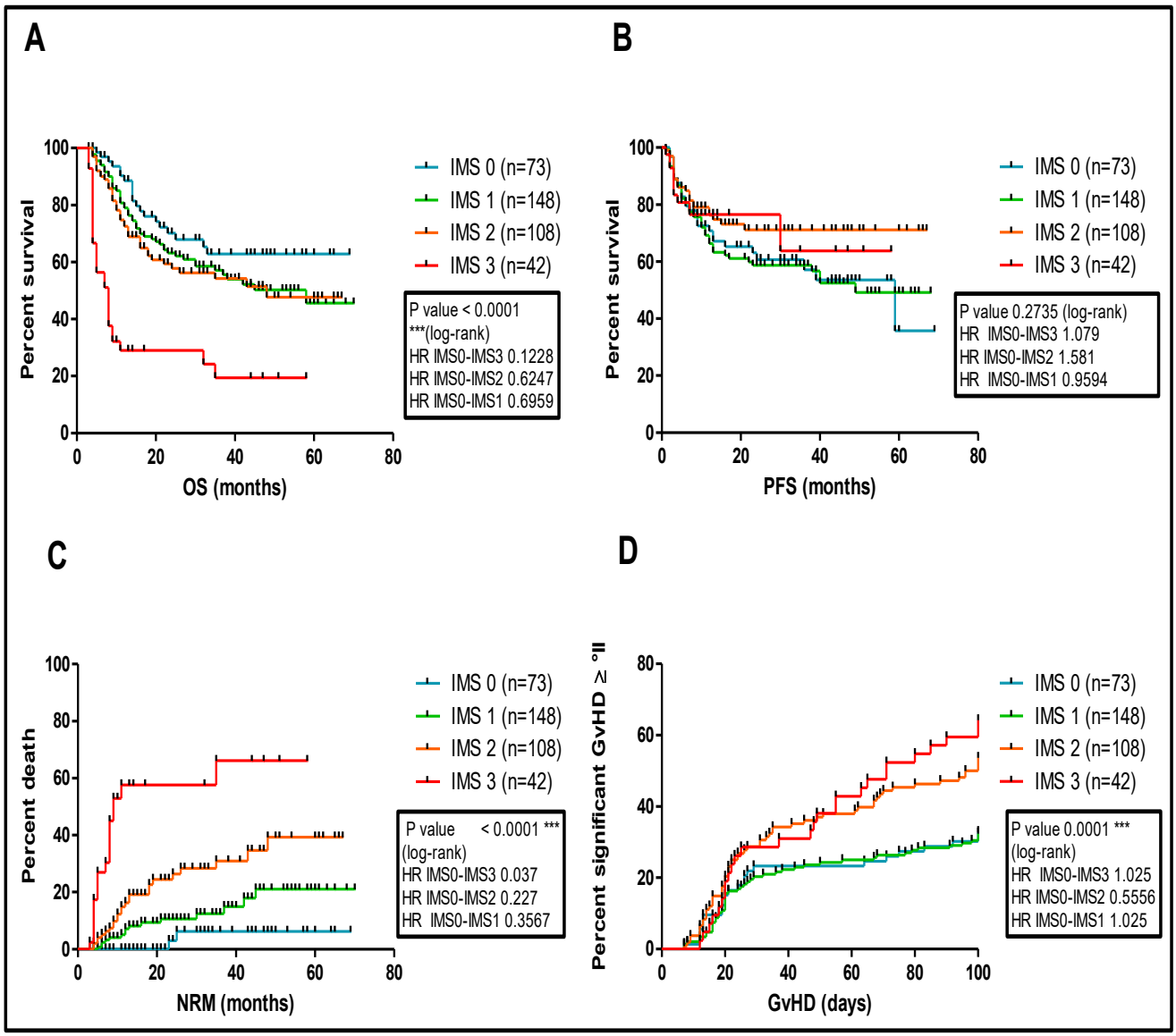


Figure 34: Survival results analysed by IMS on d+100: all recipients, no UW, n= 371: A Overall Survival (OS) of 371 recipients : according to IMS B Progression Free Survival (PFS) of 371 patients: according to IMS C Non-Relapse Mortality (NRM) of 371 patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 371 patients: according to IMS

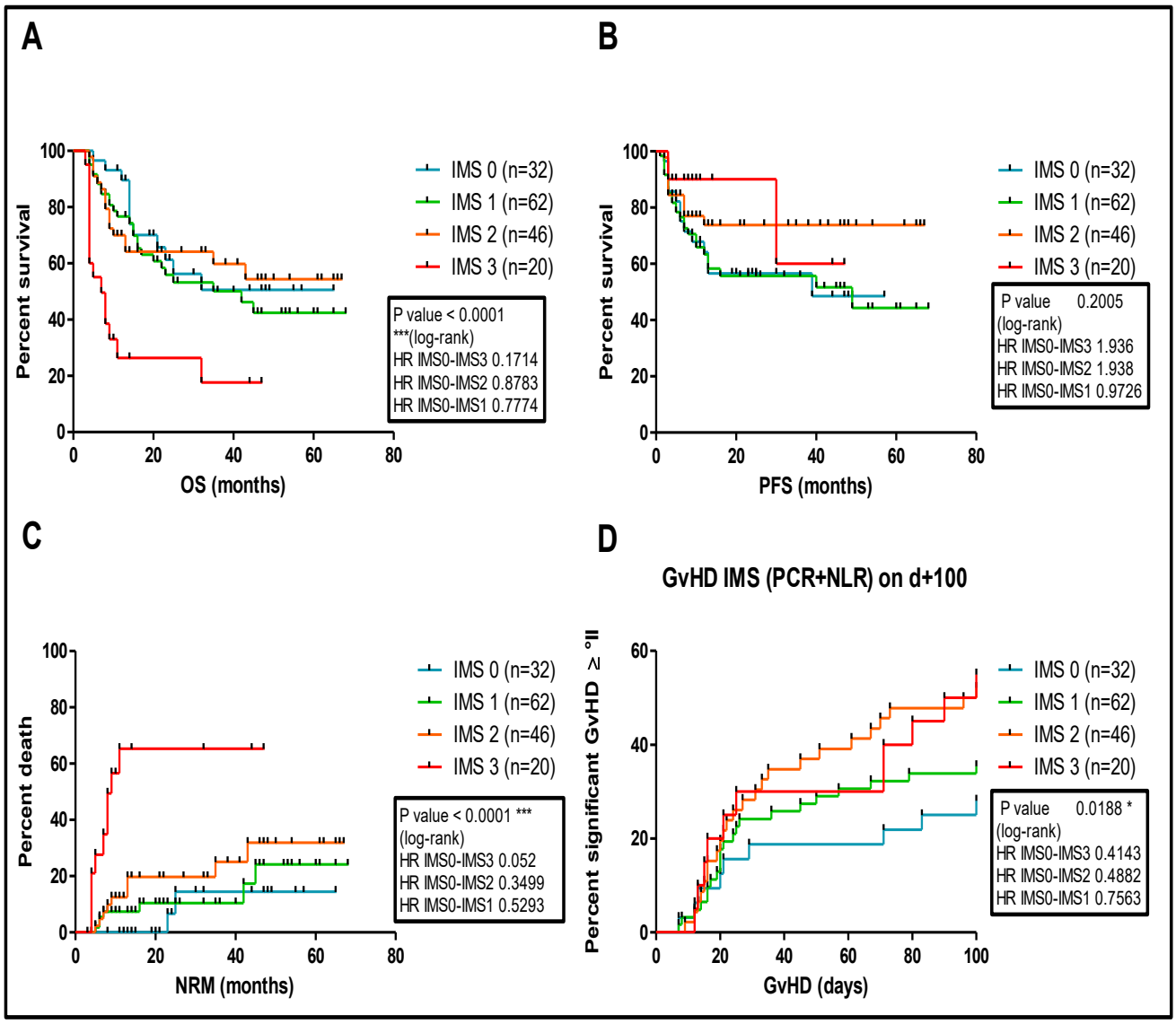


Figure 35: Survival results analysed by IMS on d+100: female recipients, no UW, n= 160 : A Overall Survival (OS) of 160 female recipients : according to IMS B Progression Free Survival (PFS) of 160 female patients: according to IMS C Non-Relapse Mortality (NRM) of 160 female patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 160 female patients: according to IMS

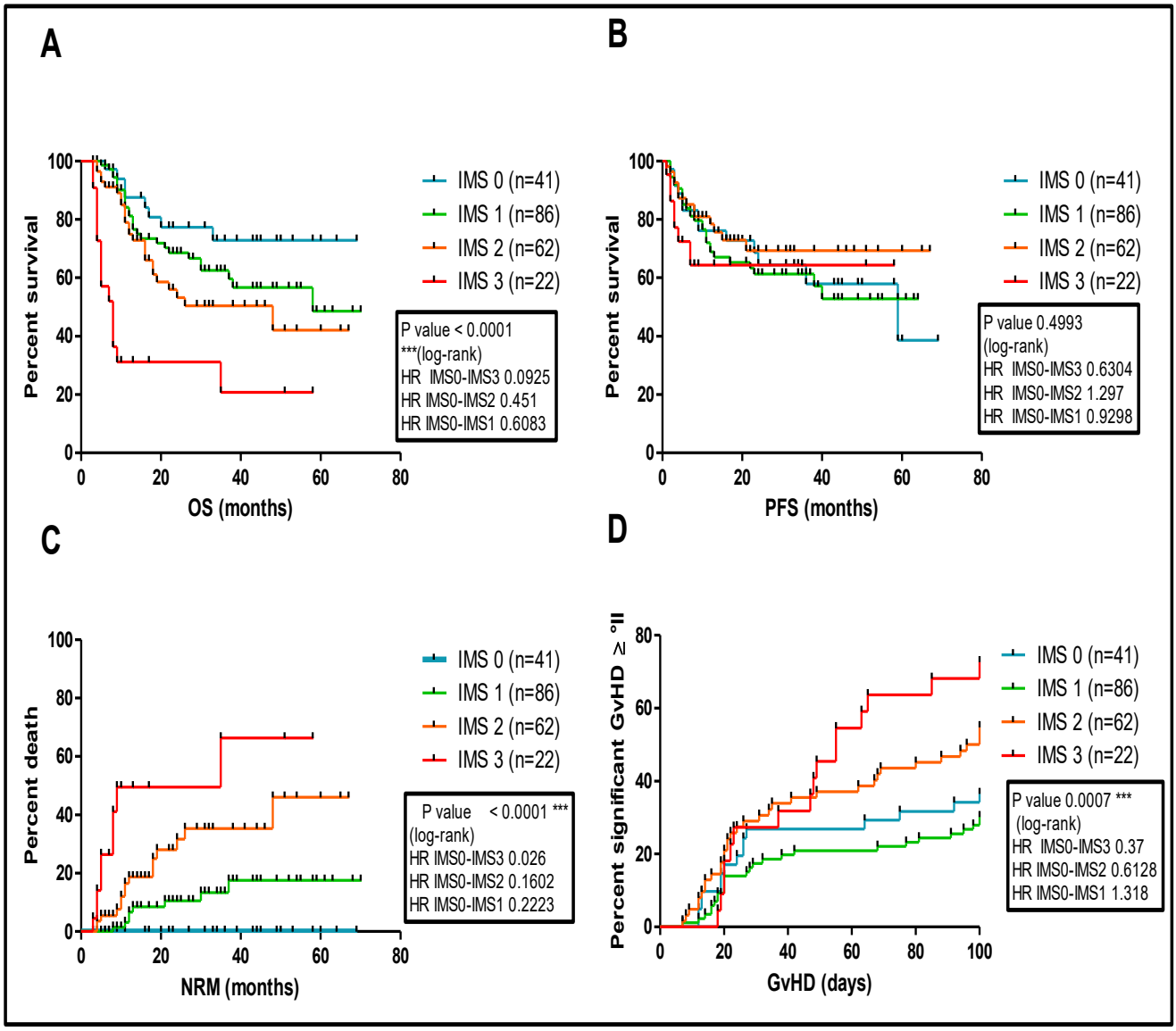


Figure 36: Survival results analysed by IMS on d+100: male recipients, no UW, n= 211: A Overall Survival (OS) of 211 male recipients: according to IMS B Progression Free Survival (PFS) of 211 male patients: according to IMS C Non-Relapse Mortality (NRM) of 211 male patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 211 male patients: according to IMS

4.7.4 Clinical outcomes according to IMS on d+100 with NLR 2: subgroup analysis with RIC, 10/10 HLA and pBSC, without UW

The median survival in the IMS 1 is 42 months and 8 months in the IMS 3. This was not measurable for the different IMS groups. The OS in the IMS 0 is 61.65% after 60 months, 38.29% of the IMS 1, 51.49% of the IMS 2 and 27.35% of the IMS 3 (after 58 months). The PFS in the IMS 0 is 37.47% after 60 months, 42.63% in the IMS 1, 75.72% in the IMS 2 and 78.97% in the IMS 3 (after 58 months). These are the NRM results: 90.62% in the IMS 0, 74.42% in the

IMS 1, 63.56% in the IMS 2 and 38.88% in the IMS 3 after 58 months. Within 100 days, 25% of the IMS 0 develop a significant aGvHD, 29.88% of the IMS 1, 59.67% of the IMS 2 and 65.38% of the IMS 3 (see Figure 37).

In females, the median survival in the IMS 1 is 35 months and 8.5 months in the IMS 3. These was not measurable in the groups 0 and 2. The OS in the IMS 0 is 54.45% after 60 months, 34.98% in the IMS 1, 67.12% in the IMS 2 and 31.25% in the IMS 3 (after 47 months). The PFS in the IMS 0 is 51.76% after 57 months, 34.15% in the IMS 1 after 60 months, 77.21% in the IMS 2 after 60 months and 91.67% in the IMS 3 after 47 months. These are the NRM results: 77.21% in the IMS 0, 70.08% in the IMS 1, 83.51% in the IMS 2 and 40.18% in the IMS 3 (47 months). Within 100 days, 22.2% of the IMS 0 develop a significant aGvHD, 37.84% of the IMS 1, 50% of the IMS 2 and 64% of the IMS 3 (see Figure 38).

In males, the median survival in the IMS 1 is 58 months, 48 months in the IMS 2 and 8 months in the IMS 3. This was not measurable for the IMS 0. The OS in the IMS 0 is 66.57% after 60 months, 44.24% in the IMS 1, 40.23% in the IMS 2 and 23.81% in the IMS 3 (after 58 months). The PFS in the IMS 0 is 38.63% after 60 months, 47.42% in the IMS 1, 74.8% in the IMS 2 and 68.75% in the IMS 3 after 58 months. The NRM in the IMS 0 is 100% after 60 months, 78.45% in the IMS 1, 49.22% in the IMS 2 and 37.62% in the IMS 3 after 58 months. Within 100 days, 26.6% of the IMS 0 develop a significant aGvHD, 24% of the IMS 1, 56.76% of the IMS 2 and 78.57% of the IMS 3 (see Figure 39).

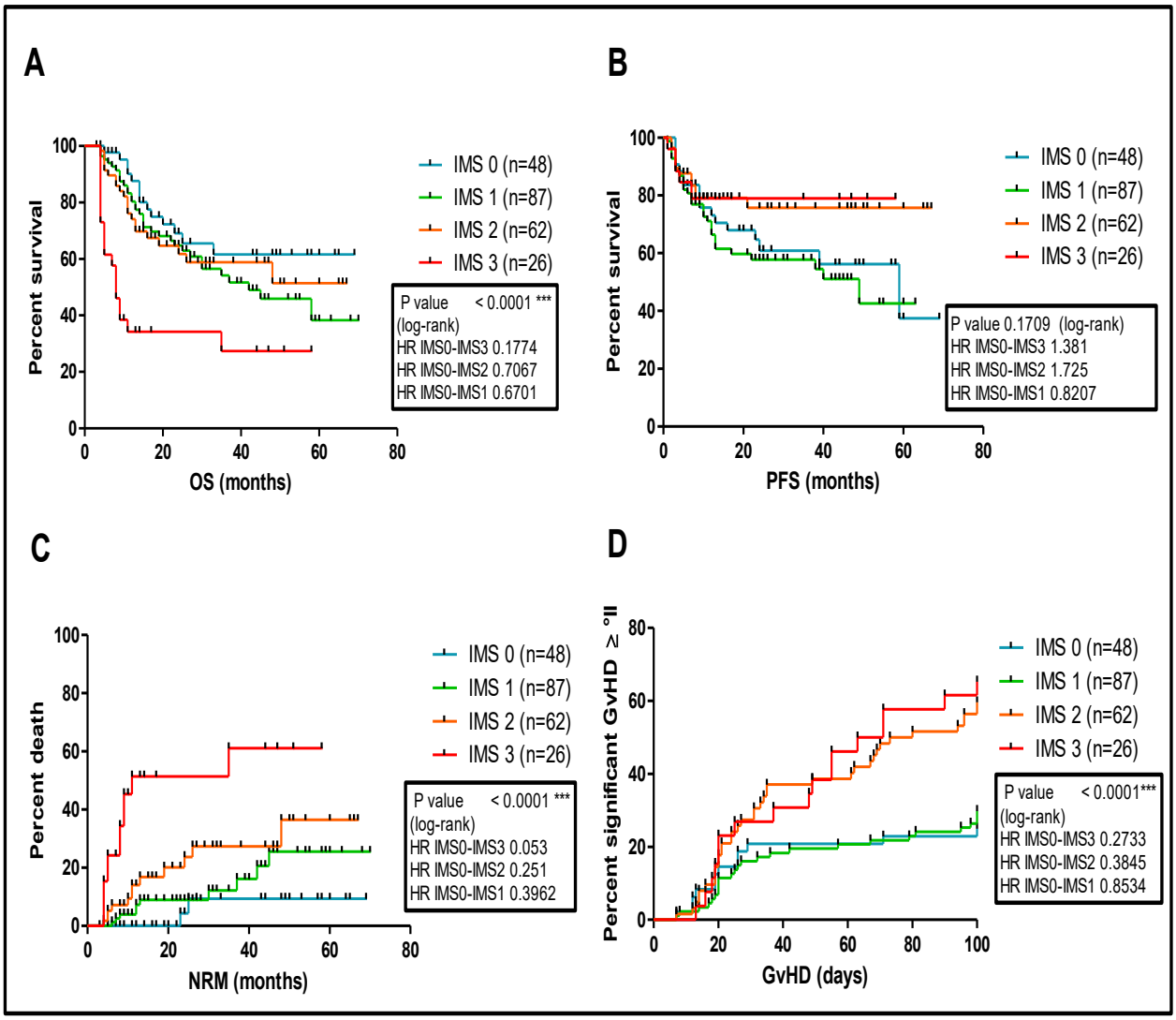


Figure 37: Survival results analysed by IMS on d+100: all recipients, RIC and matched HLA, no UW, n= 223; A Overall Survival (OS) of 223 recipients with RIC and matched HLA : according to IMS B Progression Free Survival (PFS) of 223 patients: according to IMS C Non-Relapse Mortality (NRM) of 223 patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 223 patients: according to IMS

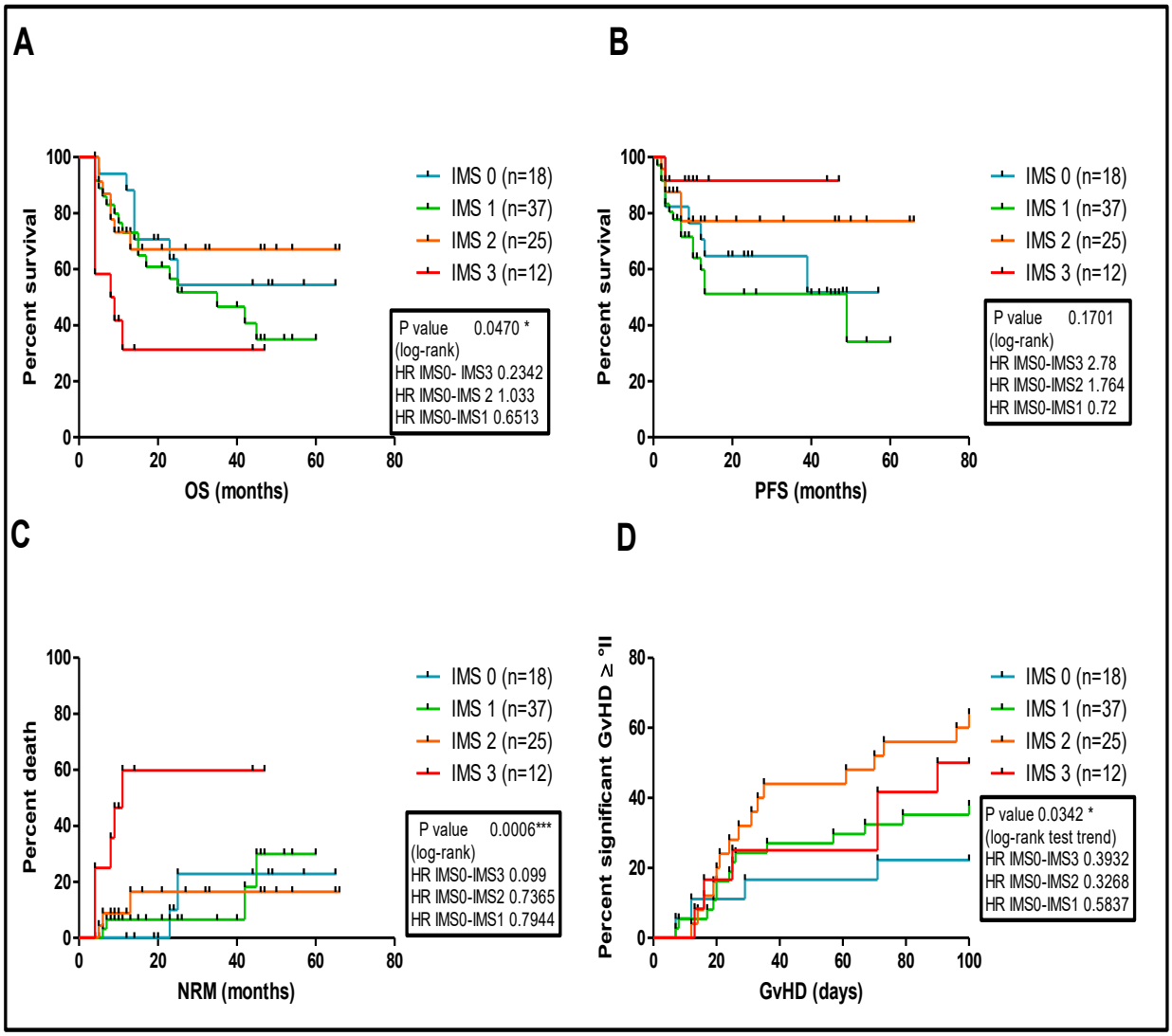


Figure 38: Survival results analysed by IMS on d+100: female recipients, RIC and matched HLA, no UW, n= 92: A Overall Survival (OS) of 92 female recipients : according to IMS B Progression Free Survival (PFS) of 92 female patients: according to IMS C Non-Relapse Mortality (NRM) of 92 female patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 92 female patients: according to IMS

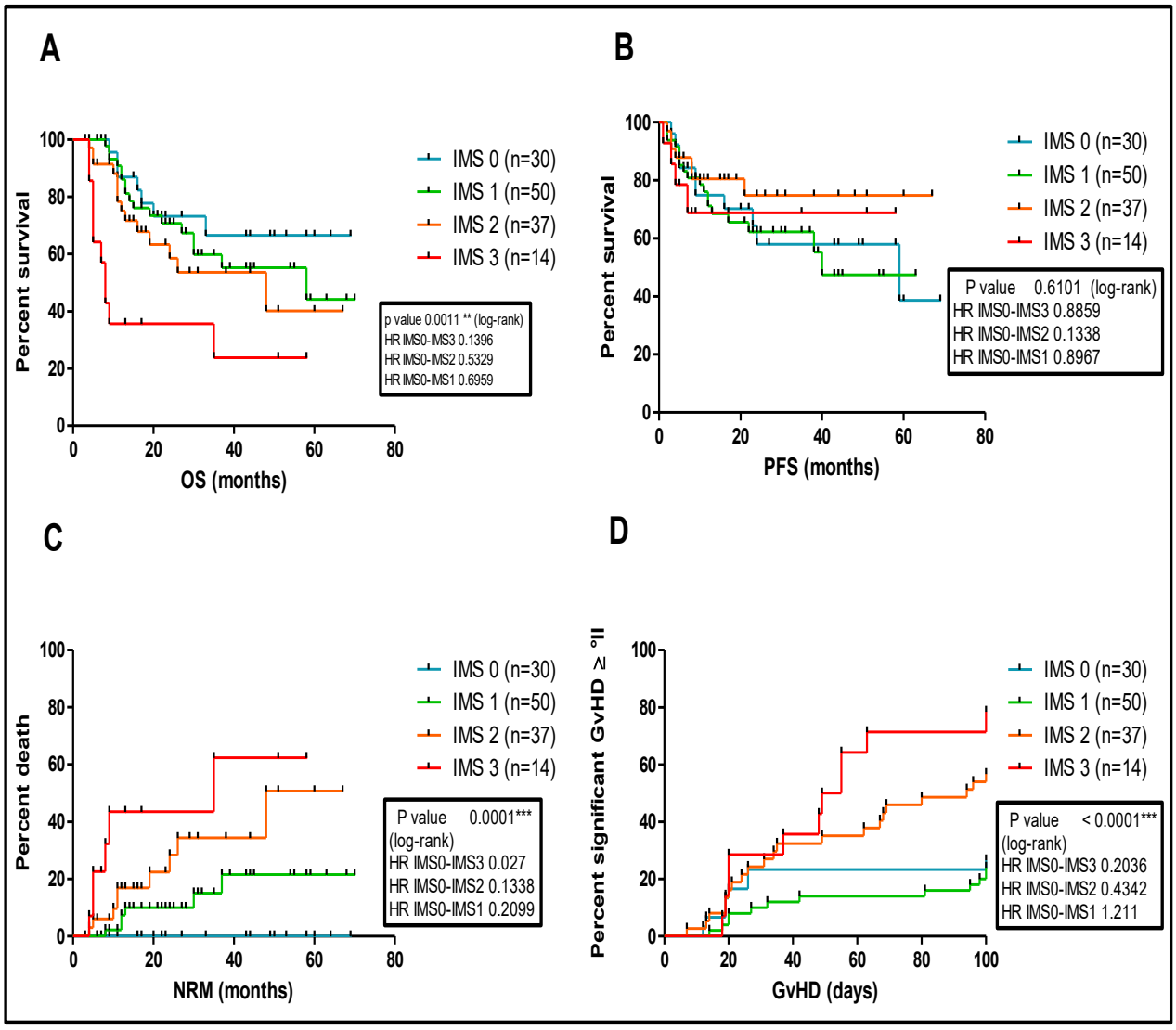


Figure 39: Survival results analysed by IMS on d+100: male recipients, RIC and matched HLA, no UW, n= 131: A Overall Survival (OS) of 131 male recipients: according to IMS B Progression Free Survival (PFS) of 131 male patients: according to IMS C Non-Relapse Mortality (NRM) of 131 male patients: according to IMS; D acute Graft-versus-Host-disease (aGvHD) of 131 male patients: according to IMS

5 Discussion

5.1 Background and overview

The main objective of this study was to analyse metabolic status as well as immune activation and their influence on clinical outcome in patients undergoing allogeneic stem cell transplantation. Our research focused on the impact of being overweight or obese as risk factors in patients undergoing alloHSCT. We looked into the variations in clinical outcomes related to increased inflammation markers such as CRP, and a high Neutrophil-to-Lymphocyte-Ratio (NLR), and malnutrition markers including hypoproteinaemia and hypalbuminaemia. Additionally, we also developed a new immuno-metabolic score to determine the correlation between clinical outcomes, malnutrition and inflammation/immune activation during the peritransplant phase. In this study, we examined the clinical outcomes of male and female patients with different BMI groups and tried to determine whether obesity was a protective or adverse factor. We also analysed whether there were gender-specific differences in survival outcomes due to fat distribution and comorbidities in male and female patients respectively.

Monitoring the patient's nutritional status during the peritransplant period has become increasingly important in predicting their clinical outcomes. Thus, several tools for evaluating the immunometabolic risk for patients undergoing alloHSCT have been developed. For example, the HCT CI Score has been established by Sorror et al in order to identify risk factors for patients undergoing alloHSCT and to predict their survival using most common comorbidities (Sorror et al. 2005). A score of ≥3 indicates a high risk of NRM. In this context, “obese patients with a BMI of >35” are assigned 1 point. HCT-CI score is calculated on patients before conditioning regimen (Raimondi et al. 2012; Sorror et al. 2015; Sorror et al. 2005).

In 2015, Sorror et al performed a prospective observational study with more than 8000 patients in the United States of America receiving their initial alloHSCT and successfully implemented the HCT CI score as a prognostic tool. Since the score was also used for risk assessment in our transplantation center, the data can be compared more easily with our results. Sorror et al found out that a high HCT CI score was linked to NRM after alloHSCT. Interestingly, “only HCT CI ≥3 were prognostic for mortality […] in RIC HC” (Sorror et al. 2015). Hence, we were interested in finding out whether obesity would be verified as a prognostic

marker for mortality in our total group and homogeneous subgroup with RIC alloHSCT too. In the following, we will discuss our clinical outcomes according to BMI, metabolic status and immune activation in detail.

5.2 Comparison of baseline patient characteristics in the pre and peritransplant setting

Parameters for our analyses were collected retrospectively. Data included 461 adult patients who were undergoing their first allogeneic stem cell transplantation. Investigation period was from 01.01.2012 to 10.11.2017 at the Cologne University Hospital. Patients had valid BMI values at point of initial diagnosis and transplantation, which can also be seen in Table 2: Overview of all examined patient demographic data and the Transplantation setting (total cohort, part 1).

The selected period of investigation included the phase before conditioning, as well as the transplant phase up until day 100 after allogeneic HSCT. We only included patients who survived until day 100, as all patients during this period had the necessary laboratory data available either during their follow-up or hospitalization. The 100th day after transplantation was the designated cut-off date for our study. This period was significant for various reasons, such as the process of engraftment, the effects of graft versus leukaemia, and the occurrence of acute graft-versus-host reactions or graft failure. Additionally, we included haemato-oncological scores, namely the Karnofsky Index in percentage and HCT-CI score, as parameters for our study. During the period of investigation BMI prior TX and at initial diagnosis was documented in all patients. Before this time period, BMI data was sampled incompletely or not at all. The reasons for gap closure might be recent research results showing the importance of complete patient examination including nutritional aspects.

The results on BMI distribution have been shown in tables 7-10, giving an overview of patient demographic data and the transplantation setting. BMI median values and averages were evaluated for total cohort, female and male cohort as well as results of BMI distribution within the homogeneous cohort (RIC -alloHSCT; n=251).

In the total cohort of 461 patients only 4.8% were underweighted (see Table 7). In contrast to underweight, the role of overweight and obesity for alloHSCT outcomes is not yet understood well.

Yang et al found out that patients with a BMI ≥23 had an increased overall survival in comparison to patients with a lower BMI.HR was significantly decreased by 40% (HR=0.60; 95% CI: 0.38-0.95) compared to underweight and normal-weight patients. 48.6% of the total cohort were normalweight, 31% were overweight and 15.6% obese patients. BMI was measured prior transplantation and at point of initial diagnosis. (Yang et al. 2017)

In our study the median BMI was changing before Tx as seen in Table 7: For the total number of patients, median BMI was 24.6 before transplantation in comparison to a median BMI of 25.4 at initial diagnosis. The results show that most patients were normalweight at the point of transplantation. The range in BMI prior Tx was 15.1-50.4 with a median of 24.6. The median in obese patients was 32.7 by a range of 30.0-50.4. Thus, we can conclude a wide range of BMI measured prior Tx with only a few individual outliers.

The Median age at transplantation was 57 years, ranging from 18 to 76 years. In contrast, within the group of underweight patients, the median age was 48 years Therefore, we determined an almost 10-year-difference in median age among those two groups.

We measured the Karnofsky-Index with a median of 90% ranging from 30 to 100% in the underweight group. In comparison, the Karnofsky-Index in the obese group was slightly higher with a median of 100% and varying from 50 to 100%, which might imply a better quality of life in patients with a higher BMI. However, our data regarding the HCT-CI score showed a median of 2 points in the total cohort, while obese patients had a median of 3 points, pointing to a higher morbidity within this group.

The main diagnosis leading to alloHSCT in the total cohort was myeloid disorders and AML in particular. Regarding the transplantation setting, we determined that 77.7% of patients were treated with reduced-intensity conditioning (RIC) and 97.2% received peripheral blood stem cells (pBSC). The calculated grafted cells (pBSCx10^6/kgBW) amounted to a median of 6.7 ranging from 1.05 to 21.85 in all patients. In comparison, obese patients were transplanted a

median of 5.37 grafted cells. Concluding from this result, patients with a higher BMI received less grafted cells per kilogram body weight.

(In the following, baseline characteristics of all female patients are described, which can be seen in Table 8 **:** 199 of all 461 patients were female (43.2%) with a median BMI of 24.6 at initial diagnosis and 23.5 at transplantation. 54.3% were normalweight, only 15 females were underweight. 24.1% were classified being overweight and 14.1% in the obese group.)

This was similar to the total cohort. Our data shows a recline regarding the BMI in the female cohort when comparing the timepoints of initial diagnosis (ID) and before transplantation (Tx). Furthermore, women showed a higher median HCT-CI Score than men (HCT-CI-Score of 3 points in the female cohort vs. 2 points in the male group, see Table 9), suggesting a higher morbidity in women undergoing alloHSCT.

There was also a difference in the weight distribution before transplantation between the male and female groups. We found out that 37% of male patients were overweight, compared to 24.1% of female patients. On the other hand, a higher percentage of male recipients were obese, with 16.8% compared to 14.1% in females. The proportion of underweight male patients was low at only 2.7%, while 7.5% of female patients undergoing transplantation were underweight. In summary, male patients had a higher BMI compared to women when undergoing alloHSCT. There was also a smaller BMI difference between the two timepoints ID to Tx in the male cohort: Whereas male recipients had lost 0.5 BMI points, female patients lost nearly twice as much at 0.9 points.

Male patients had a higher Karnofsky Index compared to female patients, with a median of 100% and a range of 50-100% as opposed to 90% and a range of 30-100%, which suggests a slightly better quality of life in the male cohort. A Karnofsky Index of 30% was observed only in underweight female patients. The distribution of stem cell source was comparable in the female and male recipients with 97 and 97.3% respectively. Regarding the amount of grafted pBSC, female recipients received a higher amount at a median of 7.03 cells x10^6/kgBW compared to a median of 6.38 cells x10^6/kgBW in male patients, an explanation for this result could be the above-mentioned weight differences in the gender specific data.

In the following, we wanted to outline the most important baseline characteristics regarding the pre-sorted, homogeneous group (see Table 10). The distribution of gender specification was similar to the total cohort: In the pre-sorted group, 40.2% were female and 59.8% male, compared with 43.2% female and 56.8% male recipients in the total cohort, respectively. The median BMI at Tx was 25.3 with a range from 18.7-45.7, while the median age at Tx was 58 years. We decided to exclude underweighted patients for the data to be more comparable. Furthermore, we also selected only patients treated with reduced-intensity therapy. Regarding the Tx setting, we only considered patients receiving pBSC as graft source and excluded patients without MRD and MUD- in order to create a comparable/ homogeneous group.

The most common diagnoses were myeloid neoplasms with 73.3% in the pre-selected homogenous group and 62.7% in the total cohort, therefore being the most significant in this analysis. AML was the most prevalent condition in both groups.

The median number of grafted CD34+ stem cells was 6.8 x10^6/kgBW in the homogenous subgroup, with a range of 2.9 to 21.85 x10^6/kgBW. Male patients had a median of grafted cells of 6.85 x10^6/kgBW, while female recipients had 6.72 x10^6/kgBW. The overall median in x10^6/kgBW of the homogenous subgroup was therefore 0.1 x10^6/kgBW higher than the total cohort. Prior to transplantation, 53.8% of patients were in complete remission, 12% received the transplant during active progression, 13.5% were actively regressing, and 20.7% were in stable active disease. In terms of BMI classification and distribution, 45.4% of the 251 patients in the homogeneous subgroup were normalweight. Interestingly, the distribution of genders was different, with almost half of female patients classified as normal weight (49.5%), while 42.7% of male patients were classified as normal weight. The percentage of overweight and obese was higher in male recipients than female recipients, with 40% of male patients and 31.7% of female patients being overweight. In summary, male patients within the homogenous subgroup undergoing alloHSCT had a higher average BMI class.

Our findings indicate that the BMI was affected by conditioning and cancer treatment therapies. There was a reduction in weight (resulting in a lower BMI) from the time of initial diagnosis up to the date of transplantation. Furthermore, the data suggests a correlation between receiving a cancer diagnosis and gaining health awareness in the process. Subsequently, changes in weight and nutritional status due to factors such as diet, side effects

of chemotherapy or even disease progression are observed in patients. As a result, there is a need for further research on the nutritional status of patients undergoing alloHSCT and multicentral studies are necessary. The proportion of overweight and obese male patients undergoing alloHSCT is higher than that of female patients. We can infer from our findings that obesity is more common in male recipients as well as should be considered and communicated as an important risk factor. In addition, changes in fat distribution and other relevant factors in this regard should also be analysed in the transplant setting.

(Patients, who received alloHSCT from 2012 up until 2017, were on average 58 years old.) Patients undergoing immunological treatment therapies and receiving alloHSCT are remarkably growing older. As mentioned above, AML and myeloid neoplasms in general were the main diagnoses within our cohorts, which was coherent with other studies suggesting it to be the most common indication for alloHSCT (Loke et al. 2020). Loke et al. described one of the reasons for an increasing number of transplantations performed: Reduced intensity conditioning (RIC) regimens ameliorate transplant toxicity, so that the number of transplant-eligible patients has dramatically increased. To further investigate the outcome using this regimen, we developed the homogeneous subgroup with RIC only. This is discussed further in the following chapter.

5.3 Clinical outcomes according to BMI, nutritional and immunometabolic scores in total and homogeneous subgroup

The main findings related to the clinical outcomes of 461 recipients according to BMI had the following results: There was a tendency towards higher survival rates with a higher BMI in the complete cohort as well as in the subgroup analyses. The 143 patients who were classified overweight (OW) prior to the transplant, had a considerably improved overall survival rate of almost 60% after five years. This effect was not observed in obese (OB) patients. Additionally, these patients also had better rates of NRM and aGvHD-I with GvHD >II°. Interestingly, in the female cohort, both pretransplant OW and OB patients had improved overall survival rates and the highest aGvHD-I. However, these benefits were only attributed to females. Pretransplant OW male patients had significantly better overall survival rates with a five-year survival rate of 60% compared to 33% and 20% in normal weight (NW) and obese patients,

respectively. Furthermore, male OW patients had better NRM rates, while obesity in men correlated with worse NRM rates. It is important to note that pretransplant overweight cannot be considered equivalent in female and male patients, as shown in figures 3, 5 and 6. Therefore, we suggest females and males to be evaluated separately as well as the introduction of gender-specific risk assessment scores or predictions.

In the following, the main findings regarding clinical outcomes according to BMI in the homogenous subgroup are described, which are referenced in figures 7-9. Similar to the total cohort, OW patients in the homogenous subgroup had improved survival rates and lower NRM rates compared to NW and OB patients. Gender-specific analysis revealed that OW and OB female patients had on the one hand the highest incidence of aGvHD-I, but on the other hand also a survival benefit. OW male patients had improved survival outcomes as well compared to NW and OB male patients. The total cohort and homogeneous subgroup analyses showed comparable gender-specific outcomes. Notably, within the homogenous subgroup the 5-year-survival in OW male patients was considerably higher at 65%, compared to 33% in NW and 25% in OB male patients. Similarly, the 5-year-NRM rate was significantly lower (p-value 0.0048**) in OW male patients (20%) compared to NW male patients (over 40%) and OB male recipients (around 50%). These findings suggest that OW patients had better survival and lower NRM rates than NW and OB patients, particularly in male recipients.

In summary, the results show a substantial impact of overweight and obesity on the survival outcomes following alloHSCT. Before the transplant, being overweight was associated with a favourable prognosis. However, there were noticeable variations between genders: Obesity appears to have a beneficial effect only in women, whereas it was an adverse risk factor in men. Therefore, the risk assessment for male and female patients should be done separately, and a gender-specific risk assessment score should be established. We suggest factoring in body composition as well as fat distribution in addition to BMI, as obesity has been shown to have a positive effect on the prognosis of women but not men in our cohort.

Could obesity have a beneficial effect in females? One explanation could be the difference in fat distribution between genders: Women tend to have a higher percentage of body fat, but it is concentrated in the gluteal-femoral area, whereas men store fat in visceral depots (Blaak 2001). Furthermore, body composition differs between genders, with women having more fat and men having more muscle mass (Schorr et al. 2018). According to Schorr et al., the health

consequences of fat distribution vary between sexes. Visceral fat, the male pattern of fat distribution, is associated with a higher cardiometabolic risk profile than in similarly aged women with the same BMI. Conversely, Schorr et al. suggests that lower extremity fat, which is more prevalent in women, has a protective effect. In general, there is a positive correlation between all-cause mortality and visceral fat (Katzmarzyk et al. 2012). Moreover, visceral fat in cancer patients has been linked to adverse outcomes and progression due to immunometabolic changes leading to insulin resistance and alterations in endocrine pathways (Yip et al. 2015; Fujiwara et al. 2015). These findings support our hypothesis that the survival outcomes of males and females should be analysed separately, as only visceral fat appears to be associated with adverse outcomes.

Several studies have highlighted the significance of body composition parameters such as bioelectrical impedance analyses (BIA), computerized tomography, and ultrasound in alloHSCT outcomes (Chughtai et al. 2016, Farias et al. 2013, Pereira et al. 2021). Pereira et al. found out that the amount of visceral fat measured by ultrasound directly correlated with a higher mortality within the first 100 days. Obesity was identified as a risk factor for mortality and we concur with Pereira on the higher mortality rates observed in the male cohort.

Our study was limited to the use of body weight and height as the only metric values regarding body composition during the investigation. Although the BMI is commonly used as a marker in oncology, it provides limited information on body composition or modifiable nutritional markers such as bioelectrical impedance analysis (BIA). In examining the influence of BIA and BMI on alloHSCT outcomes, Urbain et al. showed that overweight patients (BMI percentiles ≥90) had a higher risk of non-relapse mortality (Urbain et al. 2013). A reduced phase angle measured by BIA was found to reflect the amount of muscle mass and loss thereof. Patients who had low phase angles before transplantation were at a higher risk of death within the first two years post Tx (Norman et al. 2010).

Currently, there is significant progress in diagnostic resources and standardisation of body composition assessment in the alloHSCT setting. Further research is needed to determine the roles of BMI, BIA and computerised tomography in understanding the relationship between body composition and survival outcomes. Variations in definitions of obesity and the diversity of patient cohorts could account for differences in survival outcomes observed in international studies.

Nikolousis et al. reported results that were similar to our findings with a trend towards high BMI being associated with improved overall survival. In contrast to our results, the rate of acute GvHD in Nikolousis' cohort was lower in the high BMI group. (Nikolousis et al. 2010)

A meta-analysis by Nakao et al. revealed that obesity before transplantation was linked to increased aGvHD-I and poorer survival rates. We agree with Nakao that overweight patients have a higher risk of aGvHD, which could be related to drug dosing in chemotherapies and conditioning regimen, stem cell infusion rates and GvHD prophylaxis (Nakao et al. 2014).

Singhal et al. made therapeutic adjustments for weight by using ideal body weight (IBW) rather than the calculated BMI for chemotherapy dosage (Singhal et al. 2006). Patients with an ideal body weight from 95% to 145% had improved survival rates and overweight patients did not have a significantly higher risk of death (Doney et al. 2019).

The high incidence of aGvHD-I in overweight patients can be attributed to various factors at the metaflammatory level. Adipocytes in overweight individuals secrete significantly more adipocytokines, increase the production of inflammatory cytokines, and trigger an immunological response that leads to the proliferation of T-regulatory cells. (Hasenkrug 2007; Rosa et al. 2007; Fuji et al. 2009).

Additionally, obesity can induce a shift in the composition of adipose tissue resident-immune cells, thereby potentially increasing the alloimmune reaction following alloHSCT (Heinbokel et al. 2013). In our study, we observed that survival rates were higher in the overweight population, but not in the obese cohort.

Fuji et al. showed that the overweight group is at a significantly higher risk for GvHD as well as NRM. In comparison, the overweight group also showed a higher risk for GvHD in our results, while a higher risk for NRM was only valid for obese patients, since overweight patients had the lowest risk for NRM. We agree with Fuji et al. that the higher risk of NRM in obese recipients might be due to an increased risk of GvHD and related complications. One possible explanation for the different results is that the Fuji et. al cohort consisted exclusively of Asian patients and the average BMI in Japan being typically lower than in Caucasian countries. This BMI difference could result in less comparability between the overweight groups, whereas the results regarding obesity are similar. (Fuji et al. 2014)

5.4 Impact of the nutritional status in the peritransplant period of alloHSCT

To the best of our knowledge, this is the first study to evaluate the role of immuno-metabolic scores (GPS and IMS) measured in peritransplant setting as prognostic markers.

The Modified Glasgow Prognostic Score was measured for each patient before transplantation. The score was constructed according to the parameters outlined by Altay et al and Forrest et al. Patients were then divided into four groups based on their scores (see Table 5):A score of GPS 0 was assigned to patients with a blood serum albumin level ≥35 g/l and CRP ≤10 mg/l. Patients with an albumin level ≥35 g/l and CRP >10 mg/l were classified as GPS 1a, while those with an albumin level < 35 g/l and CRP ≤10 mg/l were classified as GPS 1b. Patients with albumin levels <35 g/l and CRP >10 mg/l were classified as GPS 2.

We utilized the Kaplan-Meier estimator and log-rank tests to analyse clinical outcomes, comparing both the total cohort and homogeneous subgroup. Among the 459 patients who had appropriate laboratory values prior to transplantation, 56.7% were classified as GPS 0 due to their low inflammation (CRP level) and high albumin level. To ensure comparable statistical data, we combined GPS groups 1a and 1b into one group. In the total cohort, the median OS was 35 months for GPS 0, 30 months for GPS 1, and 21 months for GPS 2. However, there were no significant differences in 5-year survival rates when analysing OS, PFS, NRM, and aGvHD-I (see Figure 10). Interestingly, there were statistically significant results in the homogeneous subgroup analysis (see Figure 11): GPS 0 had significantly improved survival in both male and female patients (n=147) with a p value of 0.0428*. In the homogeneous subgroup with RIC and matched HLA the median survival for GPS 0, 1, and 2 was 49, 26, and 19 months respectively. The 5-year-OS was 45.2% for GPS 0, 28.8% for GPS 1(a and b), and 41.3% for GPS 2. The incidence of aGvHD ≥II° was highest in patients with hypalbuminaemia (GPS 1b and 2) and lowest in patients classified as GPS 1a with high albumin and CRP levels. Our conclusion is that there is an influence of inflammation and nutritional status before transplantation, and malnutrition (hypalbuminaemia) can result in increased GvHD reactions.

The Modified Glasgow Prognostic Score (GPS) was also used to analyse clinical outcomes during the grafting period, specifically on day 100 after alloHSCT. Patients with combined malnutrition and inflammation had, regardless of gender, the worst 5-year survival trend and highest NRM and aGvHD-I rates. Median overall survival was longest in GPS 0 with 20 months

(see Figure 12, p value 0.001*** log rank), the same survival trends were observed in the corresponding female cohort. Interestingly, there were no deaths from any other cause but relapse among female patients classified as GPS 0 after 5 years (see Figure 13). As described in the previous paragraph, GPS 0 represents good nutritional status with normal Albumin levels and no signs of inflammation. The distribution pattern was the same in the female cohort regarding overall survival. In summary, the GPS classification seems to be significant for survival predictions. The results for the male patients (n=61) according to modified GPS and clinical outcome showed significant results too, particularly regarding the NRM rates (see Figure 14, p value of 0.0218*). The distribution in males was different compared to females though, with GPS 2 having the highest NRM rates with >80% patients dead after 60 months. The lowest percentage rates of death were seen in GPS 1a and 1b.
We therefore conclude that the small cohort number was a limitation of the study, and larger center studies are required to validate the results. Furthermore, the modified GPS did not seem to be accurately prognostic for survival in male patients.

The clinical outcomes according to GPS on d+100 in our homogeneous groups showed significantly better survival rates, progression-free survival, and the lowest NRM rates in GPS 1a. However, this distribution was only applicable to the total homogeneous subgroup, while gender-specific analyses revealed a different distribution. However, there was only a small number of patients from the total cohort which were assigned GPS 1a. In the female subgroup, only one recipient was classified as GPS 1a, which resulted in the merging of GPS 1a and 1b into GPS 1. We believe the small patient numbers resulted mainly from the lack of valid laboratory data 100 days post-transplantation.
Despite the small patient cohort, it was found that GPS 2 was consistently associated with the worst survival rates, highest NRM rates, and aGvHD-I in each group (see Figure 15, Figure 16 Figure 17). Therefore, we can conclude that both systemic inflammation and malnutritional state are adverse risk factors for the survival of patients treated with alloHSCT, and the measurements were equally important irrespective of the investigation period (GPS prior Tx and on day 100).

Survival results were also analysed on day 30 with all recipients and with the homogeneous subgroup. GPS could be measured for 439 of 461 persons. Total cohort showed <0.001 *** significance in log-rank test, depicted in Kaplan-Meier graphs, regarding OS and NRM rates

(see Figure 18). By far worst survival rates with a median of 8 months could be seen in GPS 2, in contrast to 58 months in GPS 0, and 38 months median survival in GPS 1. This distribution was reflected similarly in NRM rates. NRM rates were also better in GPS 0 and 1. Log-rank was also significant in OS and NRM analyses considered female and male cohorts, separately (p value <0.001 ***, as you can see in Figure 19 and Figure 20). In other words, modified GPS provided prognostic characteristic also in our cohort. Interestingly, for the homogeneous subgroup, this distribution according to score classification on day 30 could not be transmitted one-to-one; which can be seen in Figure 21, Figure 22 and Figure 23. Nevertheless, GPS 1 and GPS 0 had improved overall survival rates in all, female and male subgroup analyses. In conclusion, GPS, known to be a cumulative inflammation-based cancer-prognostic marker composed of serum elevation of CRP and decrease in albumin concentration, can also reflect prognoses in engraftment period (30 days post Tx). Another inflammation based prognostic marker is ratio of neutrophils to lymphocytes (NLR). The survival outcomes on day 30 were examined for all recipients as well as the homogeneous subgroup. Out of 461 individuals, GPS measurements were possible for 439. The overall cohort showed a highly significant result of <0.001*** in the log-rank test, as illustrated in Kaplan-Meier graphs regarding OS and NRM rates (refer to Figure 18). Notably, the poorest survival rates were observed in GPS 2 with a median of 8 months, whereas GPS 0 showed a median survival of 58 months and GPS 1 exhibited a median survival of 38 months. This distribution pattern was similarly reflected in NRM rates, which were also better in GPS 0 and 1.

The log-rank test also yielded significant results in OS and NRM analyses when considering the female and male cohorts separately (p value <0.00 ***, as shown in Figure 19 and Figure 20). In essence, these results confirmed that the modified GPS holds prognostic value irrespective of the patient's gender. Interestingly, for the homogeneous subgroup, the distribution based on score classification on day 30 did not align directly (see Figure 21, Figure 22 and Figure 23). Nevertheless, both GPS 1 and GPS 0 displayed improved overall survival rates in all subgroup analyses, including females and males.

In conclusion, GPS, which is known as an inflammation-based cancer-prognostic marker comprising elevated CRP levels and decreased albumin concentration, can also reflect prognoses during the engraftment period (30 days after transplantation).

Another inflammation-based prognostic marker is the neutrophil-to-lymphocyte ratio (NLR).

“NLR has independent prognostic role regarding overall […] and cancer-specific survival. It is useful for monitoring oncological therapy, including […] immune check point inhibitors treatment. NLR is a very sensitive indicator of infection, inflammation and sepsis, validated in numerous studies. Clinical research confirmed the sensitivity of NLR for diagnosis/stratification of systemic infection, sepsis, bacteraemia as well as its robust predictive and prognostic value. NLR should be investigated daily, and follow-up its absolute values and dynamic course in acute disease or critical illness” - (Zahorec 2021).

We conducted cut-off assessments and depicted the frequency distribution on day 30 and 100. In our patient cohort, the cut-off value was determined as NLR ≤2 and >2. In order to develop a comprehensible inflammation-based cancer prognostic marker utilizing commonly accessible blood serum markers, we established the immunometabolic score (IMS). This score comprises a decrease in protein level, an increase in CRP levels and the NLR. Instead of albumin level, protein level was chosen as a component of the IMS since protein level war ubiquitously available.

Based on the modified GPS, we divided the IMS into eight subgroups, which are displayed in Table 1. IMS 0 indicates protein elevation, normal CRP levels, and NLR ≤2, while IMS 3 comprises elevated CRP levels, decreased protein concentration, and NLR >2. Data from day 30 and 100 post-transplantation was analysed to monitor the clinical progress following transplantation. A total of 445 recipients with valid markers were examined using the IMS on day 30. IMS 0 demonstrated significantly improved overall survival rates, followed by IMS 1, IMS 2, and IMS 3, respectively, with a p-value of <0.0001*** in the log-rank test. NRM rates were also lower and the incidence of aGvHD-I was reduced in IMS 0 and 1 (see figure 28), whereas approximately 50% of individuals in IMS 2 and 3 developed aGvHD. These trends were also observed in the clinical outcomes specific to gender, particularly among females (see figure 29). Interestingly, within the male cohort, IMS 1 exhibited improved survival rates, with approximately 60% overall survival, and IMS 0 showed nearly 50% survival (see figure 30) These findings were consistent when conducting analyses on the homogeneous subgroup, as depicted in Figure 31, Figure 32 and Figure 33.

IMS 2b, 2c, and 3 were characterized by elevated serum CRP levels, while 2c and 3 were defined as an additional decrease in protein levels. As a result, we can deduce that there is a correlation between chronic low inflammation and the development of graft-versus-host reactions, as well as an influence of hypoproteinaemia on clinical outcomes. The presence of inflammation and malnutrition derived from CRP and protein levels, along with a predominance of myeloid cells on day 30, indicates poor survival, high rates of aGvHD, and low NRM rates. In contrast, individuals with normal CRP and protein levels and an NLR ≤2 exhibited significantly improved survival rates. In other words, the nutritional state and a balanced ratio of neutrophils to lymphocytes appear to be prognostic markers in the context of alloHSCT.

We also conducted investigations into the clinical outcomes on day 100 post-transplantation based on IMS using the NLR cut-off values of ≤2 and >2 (see Figure 34, Figure 35 and Figure 36. Notably, IMS 3, characterized by decreased protein concentration, neutrophil dominance, and high inflammation, exhibited the poorest survival outcomes and high NRM rates. The log-rank test yielded a highly significant p-value of <0.0001*** (refer to Figure 34). When analysing the female and male cohorts separately (see figures Figure 35 and Figure 36) we observed a similar distribution of outcomes, with particularly favourable results in the male cohort, demonstrating log-rank test p-values of <0.0001***.

IMS measured at 30- and 100-days post-transplantation serves as an inflammation-based cancer-prognostic marker similar to GPS and NLS. Based on our findings, IMS can be utilized to assess risks in the peritransplantation period and may also prove valuable for monitoring oncological treatments. However, further validation through multicenter and prospective studies is necessary to solidify its effectiveness.

Multiple studies have highlighted the importance of evaluating the nutritional condition of patients prior to transplantation. Impaired nutritional status not only correlates with a lower quality of life but also leads to reduced physical activity, muscle loss, increased treatment-related symptoms, and diminished tumour response (Bozzetti et al. 2009). It can give rise to various complications and significantly impact the outcomes of transplantation (Murray and Pindoria 2009; Wang et al. 2013). In our study, patients who were well-nourished both at 30- and 100-days post-transplantation and exhibited no signs of inflammation, had notably higher overall survival rates compared to malnourished patients. The combination of malnutrition

and inflammation resulted in the poorest survival rates. Our findings align with those of El-Ghammaz et al. (2017), who utilized patient-generated subjective global assessment (PG-SGA) to differentiate between malnourished and adequately nourished individuals and reported that the presence of grade II or higher aGvHD (gastrointestinal) influences nutritional status. Our Kaplan-Meier curves demonstrate a correlation between malnutrition, inflammation, and an increased incidence of aGvHD as well.

It is well-established that patients with poor nutritional status face a higher risk of mortality (Arnaud-Battandier et al. 2004; Fuji et al. 2015). In our study, we aimed to evaluate the nutritional status of patients during the engraftment period by employing metabolic scores such as GPS and IMS. This allowed us to generate risk profiles comparing well-nourished patients to malnourished ones. However, the extent to which the nutritional status can be accurately determined using a single parameter (serum albumin or protein) needs to be questioned and should be examined in future studies.

The inflammatory responses of the host play a crucial role in the pathomechanism of tumour progression and can be identified through the presence of C-reactive protein (CRP). The Glasgow-Prognostic Score (GPS), initially developed by McMillan et al., was designed to assess chronic inflammation and malnutrition (or hypercatabolism) by measuring CRP and albumin serum levels as prognostic indicators in lung cancer patients (McMillan 2008). GPS has been validated as a prognostic tool across various cancer types, with increased CRP and decreased albumin serum levels indicating a negative prognosis (McMillan 2008). GPS is also utilized for predicting overall survival (OS) and non-relapse mortality (NRM) in the context of alloHSCT (Shibasaki et al. 2017). In our study, we investigated the impact of nutritional and inflammatory markers during the peri-transplant period, specifically on day 30 and 100 post-transplantation. We aimed to determine whether GPS can also predict OS, NRM, and the occurrence of acute graft-versus-host disease grade I (aGvHD-I) within the first three months of engraftment.

Shibasaki categorized patients into three risk groups with one-year overall survival (OS) rates of 69.8%, 48.1%, and 17.1% for GPS 0, 1, and 2, respectively (Shibasaki et al., 2017). Our findings align with Shibasaki's results in terms of pre-transplant GPS, as observed in subgroup analyses: The one-year OS rates in our patients were 77%, 61.6%, and 51.1% for GPS 0, 1, and 2, respectively. Regarding five-year survival, we noted similar trends with GPS 0, GPS 1, and

GPS 2. Patients without hypalbuminaemia and without inflammation reversal demonstrated the highest survival rates, at 45.2%, 28.8%, and 41.3%. For one-year NRM according to Shibasaki et al., the GPS stratified recipients into three groups: GPS 0, 1, and 2, with rates of 19.5%, 29.7%, and 50.8%, respectively. In our cohort consisting of reduced-intensity conditioning (RIC) and matched HLA, the distribution of one-year NRM was as follows: 13% for GPS 0, 14% for the group with hypalbuminaemia and CRP ≤10 mg/L (GPS 1b), 21.7% for the group with normal albumin and increased CRP >10 mg/L (GPS 1a), and 34.3% for GPS 2. Based on our results, it can be inferred that inflammation (CRP >10 mg/L) within the respective risk groups is associated with increased NRM.

Proctor et al. conducted a meta-analysis focusing on the comparison of various inflammation-based scores. Within their study, they examined the predictive value of the modified GPS. Unlike the standard GPS, the mGPS utilizes a distinct classification system: mGPS 0 is characterized by a CRP level of ≤10 and an albumin level of ≥35 or <35, mGPS 1 is defined by an albumin level of ≥35 and a CRP level of >10, while mGPS 2 is characterized by an albumin level of <35 and a CRP level of >10. (Proctor et al. 2011)

Proctor et al. demonstrated the predictive ability of the modified Glasgow-Prognostic Score (mGPS) in determining cancer-specific outcomes. Their findings indicate that the mGPS is particularly effective in distinguishing between groups with different prognoses, specifically identifying those with favourable and unfavourable outcomes. The results of Proctor et al. highlight the significant impact of systemic inflammatory response on the interaction between nutritional decline and poor survival in cancer patients (McMillan 2009). The crucial factor in this relationship, as identified by Proctor et al., is the level of C-reactive protein (CRP). Consequently, it is recommended that CRP-based scoring systems be routinely employed in the assessment of cancer patients, with the aim of targeting and managing systemic inflammatory response as a future therapeutic approach (Proctor et al. 2011).

We developed the immunometabolic score (IMS) as an additional scoring system similar to the modified Glasgow-Prognostic Score (mGPS) but incorporating the neutrophil-to-lymphocyte ratio (NLR). Total protein was measured instead of serum albumin since these parameters were more commonly available in our patients' laboratory values. Patients with NLR ≤2, no inflammation, and good nutritional status exhibited significantly better survival rates. On the other hand, patients with NLR >2, high inflammation, and malnutrition

experienced inferior overall survival rates. Moving forward, further validation of the IMS is necessary, including testing it on larger cohorts to assess its effectiveness in predicting survival outcomes in alloHSCT. With continued research, we hope to establish the IMS as an additional inflammation-based cancer-prognostic marker.

5.5 Restrictions and limitations

Patients in our cohort underwent different conditioning regimens and had varying comorbidities, which can impact the outcomes and survival following alloHSCT. It is important to note that our study was conducted at a single center and with a retrospective design. To gain more comprehensive insights, future research should include follow-up studies with larger and more homogeneous patient groups, as well as prospective randomized studies.

While our results provide insight regarding survival patterns and the impact of inflammation on allogeneic stem cell transplantation, it is crucial to acknowledge that subgroup analyses with homogeneous groups were limited to small patient numbers. Therefore, conducting larger, multicenter studies would be beneficial. Comparisons on an international scale are challenging due to the lack of standardized weight definitions and variations in pretransplant settings. We recommend establishing multicenter studies or larger cohort studies focusing on a specific diagnosis for alloHSCT, while defining a homogeneous cohort with consistent use of reduced-intensity conditioning, peripheral blood stem cells, and similar pretransplant protocols.

5.6 Conclusion

Improved immunometabolic risk measures surpassing the limitations of BMI are required for patients undergoing alloHSCT. Our findings suggest that pretransplant scores such as GPS and NLR could hold value in estimating risks, but further validation is necessary. To achieve this, larger multicenter studies are needed to validate the Immunometabolic Score (IMS).

In recent years, there has been a rise in the number of elderly patients undergoing alloHSCT, with AML patients comprising the largest group. It is crucial to collaborate with experts in nutritional medicine to develop additional scores or markers for pretransplant risk assessment. With the expanding therapeutic options, there is a need to enhance measurement tools that predict nutritional status, such as standardizing radiological measurements which assess fat distribution, identifying markers of malnutrition and also developing sex-specific scoring systems. Accomplishing this will require improvements in routine examinations, treatments, and conditioning therapies prior to transplantation.

Further validation of risk estimations is essential for the benefit of all patients undergoing alloHSCT.

5.7 Summary and Outlook (German)

Das Gewicht vor allogener Stammzelltransplantation scheint nachweislich einen Einfluss auf Überlebensergebnisse zu haben. Die Daten dieser Doktorarbeit zeigen, dass vor allem die übergewichtigen, männlichen Patienten mit einem BMI zwischen 25 und 29,9 das beste Überleben haben. Bei der weiblichen Kohorte zeigte sich ein Überlebensvorteil in allen übergewichtigen, auch den fettleibigen Patientinnen. Fettleibigkeit ist des Weiteren mit der höchsten akuten GvHD-Inzidenz assoziiert. Faktoren wie der Ernährungszustand und systemische Entzündungsreaktionen scheinen ebenfalls Auswirkungen auf das Überleben nach Stammzelltransplantation zu haben. Vor allem die Untergruppe aus Patienten mit einer Mangelernährung und hohen Entzündungswerten zeigen geringes Überleben, eine hohe NRM und entwickeln am häufigsten eine aGvHD. Diese Ergebnisse zeigten sich unabhängig vom Zeitpunkt der Messung. Diesen Trend kann man auch anhand der Ergebnisse des immunometabolischen Scores ablesen. Hier erkennt man ebenso unabhängig vom Zeitpunkt der Messung, dass die Gruppen mit hohen Entzündungswerten, Malnutrition und einer Neutrophilen-Lymphozyten Ratio größer als 2 das geringste Überleben und die höchste aGvHD- Inzidenz zeigen. Bisher ist es wissenschaftlich wenig untersucht, ob Übergewichtigkeit einen negativen oder positiven Einfluss auf das Überleben nach Stammzelltransplantation hat. Es wurde bislang als Komorbidität und Risikofaktor erfasst, so zum Beispiel im HCT-CI Score. Das Ergebnis dieser Doktorarbeit zeigt, dass Übergewicht bis zu einem gewissen Ausmaß eher ein Überlebensvorteil ist. In Zukunft müssten die Ergebnisse mit größeren, multizentrischen Studien validiert werden. Nicht nur das Gewicht hat einen entscheidenden Faktor auf das Überleben, sondern auch GvHD-Inzidenz und NRM. Weitere Faktoren wie Entzündungsreaktionen und der Ernährungsstatus erweisen sich als einflussreich auf oben genannte Ergebnisse. Der GPS ist bereits ein etablierter Score für Überlebensannahmen bezogen auf verschiedene solide Tumoren. Da im Gegensatz zu Albumin das Gesamtprotein laborchemisch viel häufiger erfasst wurde, stellt sich die Frage, ob der immunometabolische Score bestehend aus CRP, Gesamtprotein und der Neutrophilen-Lymphozyten Verteilung nicht auch für größere Kohorten und solide Tumoren etabliert werden könnte.

6 Appendix

6.1 List of references

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6.2 List of figures

6.3 List of tables