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Safety and efficacy of drugs used in paediatric oncology

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1. Abstract

1.1. Background

There are many areas of improvement within paediatric oncology, especially concerning the safety and efficacy of drugs used within this field. The thesis will focus on two areas of improvement: the delivery of antibiotics through elastomeric devices and the use of novel biomarkers to measure cisplatin-induced nephrotoxicity.

1.2. Aims

To identify names of antibiotics that have been evaluated to be delivered in elastomeric devices within a paediatric population and to investigate the relationship between urinary NGAL and cisplatin-induced nephrotoxicity amongst a paediatric population.

1.3. Methods

In terms of methodology, for the evaluation of antibiotic delivery through elastomeric devices amongst a paediatric population, a systematic review was performed (using PRISMA methodology), and for the evaluation of urinary NGAL to measure cisplatin-induced nephrotoxicity, pre-existing "PINGU" study data was collected and analysed to make correlations between urinary NGAL and both demographic and other urinary variables.

1.4. Results

In terms of the results discovered from the systematic review, three full-text articles were identified from our search strategy, covering seven antibiotics (ceftazidime, tobramycin, ciprofloxacin, piperacillin-tazobactam, flucloxacillin, amikacin and gentamicin) that have been evaluated to be used through an elastomeric device for a paediatric population. In terms of the efficacy of antibiotics delivered through elastomeric devices in a paediatric population, one study reported that 76% were cured of their infection, with 18% having "partial improvement" and 6% experiencing "treatment failure" (see ***Table 2*** for definitions of terms contained within quotation marks), whilst the other study shows both continuous (10.6%) and short (10.1%) infusion treatments delivered through elastomeric devices yielded similar mean increases of FEV_1 in a cohort of paediatric cystic fibrosis patients. In terms of the safety of these devices, only one study provided data specific to the adverse events caused by elastomeric devices, where only one child out of 34 paediatric patients experienced an elastomeric device failure.

In terms of the results from the analysis of PINGU data, 21 patients were included within the study, yielding a total of 394 urine samples, where urinary NGAL did not show a significant association with cisplatin use, where baseline (day 1, pre-dose) values are often being measured with the highest mean urinary NGAL levels.

1.5. Conclusions

It should be noted that although there is an abundance of OPAT and p-OPAT data in previous literature, there is a surprising lack of data regarding antibiotic delivery through elastomeric devices amongst a paediatric population. Additionally, there is a lack of clinical pharmacokinetic data regarding this topic. Although the results contained within the PINGU study are negative, previous studies have noted mixed results, where there seems to be a recommendation to focus on confounders and other variables that can potentially skew urinary NGAL to impair/promote the detection of cisplatin-induced nephrotoxicity, where an emphasis has been made for larger paediatric studies, when concerning future studies.

2. Disruptions caused by COVID-19 and other events

Originally, one of the aims of the MPhil was to progress with the ongoing POPPET (Pharmacokinetics of continuous infusion of Piperacillin/Tazobactam in children) study by obtaining blood samples for Piperacillin/Tazobactam concentrations from pre-consented paediatric oncology patients that have presented with febrile neutropaenia and determining the concentrations of Piperacillin/Tazobactam achieved when administered by continuous infusion through an elastomeric pump, however, the planned continuation of the study was deemed unfeasible due to an unprecedented pharmacy crisis (an explosion in the Alder Hey pharmacy that disrupted production of elastomeric devices) and the COVID-19 pandemic which deemed the study as a lower priority study. Due to the initial project being motivated by paediatric oncology, I was given the opportunity to perform data analysis on pre-existing data from the PINGU study, which aims to correlate the incidence of AKI and the use of chemotherapeutic drugs amongst a paediatric oncology population. Thus, combining these two projects, I hope to be able to shed some light on the safety and efficacy of both antimicrobials and chemotherapeutic drugs amongst a paediatric population.

With regards to data collection and data analysis of the pre-existing data from the PINGU study, the COVID-19 pandemic limited my time within the hospital which affected the data collection, where a significant proportion of my time was spent on finding data amidst hundreds of paper documents (case report files and patient records), where most of the data required for analysis was not on the Meditech database. Moreover, although attempts were made to find all pre-existing PINGU data, some of this data was missing (e.g., pre-dose creatinine values), which had a direct impact on the analysis of the PINGU data, especially when concerning patient demographics and their p-RIFLE stage. Furthermore, access to statistical analysis training was limited due to the COVID-19 pandemic and time constraints from restricted hospital access and the prospect of data cleaning mentioned previously.

3. Introduction

3.1. Cancer in children and young people

3.1.1. Paediatric cancer statistics

Childhood cancer is relatively rare, arising in just one out of 500 children by the age of 14, equating to around 1900 new cases being diagnosed each year in the UK (1). In the UK, childhood cancers account for fewer than 1% of all cancers; however, this figure has risen by 15% since the mid-1990s (1). Leukaemia and various brain tumours compromise the most common types of childhood cancer, with acute lymphoblastic leukaemia (ALL) being the most common form of paediatric cancer (1). This contrasts with adults, where leukaemia is the 12th most common cancer amongst adults, with breast cancer being the most common (2).

Fortunately, over 80% of young people (81% for males and 84% for females) diagnosed with cancer survive their disease for at least five years, according to statistics for 2001-2005 in the UK (3, 4). In contrast, the five-year predicted net survival of adults in the UK that have developed some form of cancer (excluding non-melanoma skin cancer) is 54.3%, according to a document published by *Cancer Research UK* in 2014 (5, 6). Moreover, since the early 1970s, mortality rates for childhood cancers have declined by 70%, with a 25% reduction in mortality rates over the past decade, showing how crucial cancer research is and its potential to reduce the mortality rate of children's cancer (1). Although children's cancer survival does not variate with age as much as cancer amongst adults, certain paediatric cancers have better survival rates at specific ages (1). Regarding risk factors of childhood cancers, lifestyle hazards potentially have a lower influence on childhood cancer relative to adult cancers; however, research on childhood cancer risks is scarce due to the relative rarity and diversity for this group of cancers (1). However, one of the most common environmental causes of developing childhood leukaemia is radiation exposure, which can be significantly affected by their current and past geographical locations (7). With regards to one of the more prevalent forms of paediatric cancers, leukaemia; hereditary abnormalities such as Down syndrome, Li-Fraumeni syndrome, and Wiskott-Aldrich syndrome are common genetic causes of acquiring childhood leukaemia (7).

3.1.2. UK paediatric cancer services

The *Children's Cancer and Leukaemia Group* (CCLG) is the UK and Ireland's specialist medical group representing all of those involved in the health care for children and young people with cancer (8). They are responsible for developing the national clinical treatment guidelines ensuring paediatric oncology patients with effective, safe, and standardised care (9). The CCLG states, "where possible, children with cancer are treated on clinical trials. However, the nature of research means that there will not always be open trials for some childhood cancers and using treatment guidelines is vital for

ensuring equality of access to what is regarded by national experts as the best possible treatment currently available" (9). Clinical trials form a large part of the progress of children's cancer treatment over the last few decades, and considering that a significant proportion of all children and young people with cancer will be treated on clinical trials, many clinical trials for the treatment of children's cancer and leukaemia have been nationally adopted through the *National Institute for Health and Care Excellence* (NICE), which directly promotes standardisation and efficacy of care for children and young people with cancer. Members of the CCLG regularly review treatment recommendations and guidance to cover all the typical children's cancers, including leukaemia (9). National experts (usually members of CCLG Special Interest Group) write guidelines for their respective fields within each cancer type, where their recommendations and guidance are drawn upon the evidence presented from treatment protocols and international research to ensure that their guidance is consistent with the international standard of care (9).

In terms of the organisation of paediatric oncology services in the UK, children and young people are often seen in both primary (GP) and secondary care (local hospital) setting prior to hospitalisation, where there is a network of tertiary specialist centres called Principal Treatment Centres (PTCs), which are responsible for the diagnosis and treatment of children's cancer (10). According to national NHS guidance, all children and young people must be referred to the PTCs if cancer is suspected (10). There are a total of 19 regional PTCs, and in most regions, PTCs may share care with units within local hospitals known as Paediatric Oncology Shared Care Units (POSCU), where the shared care will be managed through a multidisciplinary team (MDT) coordinated by the PTC (10). MDTs are led by a consultant paediatric oncologist/haematologist who specialises in the treatment of childhood cancers or leukaemia and can also include other medical professionals such as paediatric surgeons, radiographers, nurse specialists, pharmacists, dieticians, physiotherapists, occupational therapists, psychologists, and social workers (11). MDTs meet weekly to discuss newly diagnosed children, clinical trials, treatment options and any situations involving patients or their families, considering whether they need additional support (11). Furthermore, for some rare or difficult-to-treat cancers, MDTs may also occur at a national level to amass as much expertise and experience as possible from leaders of their specific fields, which ensures that the patient receives the best possible care, and the team provides more consistent decision-making (12).

3.1.3. Drugs used to treat common cancers within paediatric oncology

Therapies using drugs are also known as systemic therapies, where a specific type of medication is given through the bloodstream to reach cancer cells throughout the body (13). Systemic therapies are primarily administered either intravenously (IV), orally, intrathecally or intramuscularly, where these types of therapies include: chemotherapy and immunotherapy (13, 14). A patient may receive

one type of systematic therapy as their treatment, a combination of systemic therapies or be on a treatment plan that includes some combination of systemic therapy, radiotherapy, and surgery (13).

3.1.3.1. Chemotherapeutic, immunotherapeutic, and targeted cancer cell drugs

3.1.3.1.1. Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is the most common cancer affecting children and young people with cancer (15). With regards to this disease, common chemotherapeutic drugs used to treat ALL are dexamethasone (a glucocorticoid essential for the treatment of ALL), cyclophosphamide, cytarabine, daunorubicin, doxorubicin, mercaptopurine, methotrexate, pegaspargase (recommended by *NICE* for first-line treatment of ALL) and vincristine (14, 16, 17). Based on various characteristics, including the patient's age, white cell count, and the results of blood and urine tests performed at the time of diagnosis, the patient will be assigned to one of three treatment regimens (14). Regimen A is the least intensive therapy and is typically used as the initial treatment plan for children under ten and those with a low white cell count when diagnosed with ALL (14). Regimen B is a treatment regimen that falls between Regimen A and Regimen C in terms of severity. It is recommended for children over the age of 10 and for those with a higher white cell count initially diagnosed with ALL (14). Regimen C is the most intensive of the three regimens; it is not employed at the start of therapy but rather when there is some failure in clearing enough of the leukaemia cells after the first part of regimen A or B (14). Advancement to regimen C occurs typically when patients have a high risk of minimal residual disease (MRD) at the end of their induction phase, and once a patient has been transferred to regimen C, they will not be returned to regimens A or B. (14). The total length of treatment is over two years, with five phases (induction, consolidation, interim maintenance, delayed intensification, and maintenance), with the induction phase being the most intensive (patient will need to remain in the hospital for at least a week or two) and maintenance phase being the least intensive (potentially well enough to adhere to a normal routine) (14).

However, ALL can return during treatment or even after treatment has finished, also known as relapse (14). Fortunately, if the relapse occurs during the late stages of chemotherapeutic treatment or after the treatment regimen, the probability that a patient can be treated successfully again is increased (14). Treatment for relapsed childhood ALL includes stem cell transplants and CAR-T therapy (a form of immunotherapy) (14). With regards to CAR-T therapy, *NICE* recommends tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (the most common type of ALL) aged up to 25 years old (17).

3.1.3.1.2. Astrocytoma

Over 40% of all brain and spinal cord tumours in children and young people are astrocytomas, making astrocytomas the most common brain and spinal cord tumour in this population group (18). When considering treatment options of astrocytomas, there needs to be awareness about the four different types of astrocytomas: pilocytic astrocytoma (grade 1), diffuse astrocytoma (grade 2), anaplastic astrocytoma (grade 3) and glioblastoma multiforme (grade 4) (18). Low grade astrocytomas are classified as grade 1 and 2, whereas high grade astrocytomas are classified as grade 3 and 4 (18). Around 80% of all astrocytomas are low grade astrocytomas, which generally have a better prognosis to those who suffer from high grade astrocytomas (18). For low grade astrocytomas, the main course of treatment is surgery, which intends to remove as much of the tumour as possible. However, there are instances where this might not be possible; for example, surgery can cause irreversible injury to surrounding healthy brain tissue that other less invasive therapies such as radiotherapy, proton beam therapy and chemotherapy can be used as alternative therapies (18). For high grade astrocytomas, the curative possibilities of surgery are significantly decreased, and if surgery is still a potential treatment option, child patients are likely to receive additional treatment (radiotherapy, chemotherapy, targeted cancer cell therapy) or some combination of these therapies (18).

With regards to astrocytomas amongst children and young people, common chemotherapeutic drugs used to treat this disease are cyclophosphamide, vincristine, cisplatin, etoposide, carboplatin, ifosfamide, vinblastine, high dose methotrexate, temozolamide (over the age of 3 years old) and procarbazine (19). Specifically for paediatric patients, for low grade astrocytomas, chemotherapy drugs such as vincristine, carboplatin and vinblastine are commonly used and for high grade astrocytomas, temozolomide is commonly used (20, 21). Furthermore, there is possibility that surgeons can implant a chemotherapeutic wafer implant right after surgeons have removed some or all of the tumour, where the chemotherapy drug (carmustine) is slowly released by wafers into the affected area, over a few days (18). However, this is not a common treatment for children and young people and is mainly reserved for adults (18). When concerning targeted cancer cell therapy treatments for astrocytomas, researchers were interested in the prospect of using bevacizumab (18), a vascular endothelial growth factor (VEGF) inhibitor to treat astrocytomas in children and young people, however, according to a trial from 2013 to 2015 (adding bevacizumab to radiotherapy and temozolomide for children with high grade gliomas), “bevacizumab did not help children with a high grade glioma” (22).

3.1.3.1.3. Neuroblastoma

Although rare, 6% of all paediatric cancers are represented as neuroblastomas in the UK and primarily affects children under the age of 5 years old (23, 24). With neuroblastomas that have yet to metastasised, surgery might be the only treatment necessary, however, children and young people with neuroblastomas might require chemotherapy before the surgery to decrease the size of the tumour, which would potentially increase the safety of the operation (25). Moreover, for some children and young people who are deemed to have high risk neuroblastoma, these patients can be offered additional high dose chemotherapy and stem cell transplants (25). After surgery, some children and young people are recommended to undergo radiotherapy to reduce the risk of the neuroblastoma to relapse, where this option is more likely with patients suffering from intermediate or high-risk neuroblastoma (25).

With regards to neuroblastomas amongst children and young people, common chemotherapeutic drugs used to treat this disease are cyclophosphamide, ifosfamide, busulphan, melphalan and vincristine (25). Out of the chemotherapeutic drugs listed above, doctors will likely prescribe a combination of two or more of these drugs for children and young people with neuroblastomas (25). When concerning immunotherapies available for the treatment of nephroblastomas, NICE recommends the use of an anti-GD2 antibody (dintuximab beta) for children and young people who are at risk of their cancer reoccurring and for those who have not already had anti-GD2 immunotherapy (25). Furthermore, when concerning children with high risk neuroblastoma, retinoid treatment (13-cis-retinoic acid, isotretinoin) can diminish risk of the neuroblastoma reoccurring after stem cell transplant and high dose chemotherapy, where doctors have recommend 6 months of retinoic acid after the patient's transplant (26).

3.2. Effectiveness of chemotherapy within paediatric oncology

According to statistics published by Cancer Research UK, from 2011 to 2015, children with cancer have a relatively high 5-year or more survival rate (84%) and this rate has more than doubled since between the 1970s and 2000s (27), where chemotherapeutic drugs (amongst other treatment modalities) form a large part of the reason for the general success of treating children's cancer. This statistic highlights the improvement and effectiveness of cancer treatment.

3.2.1. Acute lymphoblastic leukaemia

When concerning ALL, the most common malignancy observed within paediatrics, survival rates of children and young people suffering from ALL have increased from less than 10% (1960s) to 90% from current reports (28, 29), where it is regarded that the first group of long-term paediatric survivors of ALL was due to the introduction of methotrexate, corticosteroids and mercaptopurine during the early 1950s (30). A significant proportion of the current success of treating ALL in children

and young people is largely based on the intensification of chemotherapeutic regimens (for patients with larger risk for relapse) and advances of diagnostic risk stratification (31), however, the rate of progress concerning survival has somewhat plateaued, with the escalation of chemotherapeutic treatment being subject to diminishing returns due to their toxicity (32). Furthermore, the substantial increase in ALL survival amongst children and young people can be attributed to 2 aspects, the first being a 44% decrease of risk of death from disease progression and relapse, and the second being that the more common sub-type of ALL (B-cell ALL) has a significantly higher 5-year survival than children and young people suffering from T-cell ALL (28). Assimilating all the points mentioned above, the advances in chemotherapeutic treatments directly benefits paediatric populations by preventing disease progression, where relapse itself remains an area for further improvement and a serious adverse event (28, 33, 34).

Although the knowledge on risk factors influencing ALL has been known for many years, ALL survival rates in children and young people have increased due to a better understanding of the molecular genetics of leukaemic cells, which has led to targeted therapies (such as imatinib and other ABL-class inhibitors) for the treatment of B-cell ALL that express the BCR-ABL1 translocation (also known as the Philadelphia chromosome) (31). Looking at other more recent advancements, the development of immunotherapeutic agents that target B-cells have significantly impacted the care of paediatric patients with refractory and relapsed B-cell ALL (31). Examples of these targeted immunotherapeutic drugs are tisagenlecleucel (66% overall survival rate at 24 months, treated for refractory/relapsed B-cell ALL) (35, 36), (79.4% overall survival rate at 24 months, treated for refractory/relapsed B-cell ALL) (37) and inotuzumab (58-67% complete response rate, treated for refractory/relapsed B-cell ALL) (38, 39), where data was obtained from clinical trials that compared the immunotherapeutic drug with chemotherapy versus chemotherapy alone, deeming them more efficacious compared to using standard chemotherapy alone (31).

3.2.2. Low grade glioma

Although surgery remains first-line treatment for low grade glioma (LGG) and is considered as a curative treatment (8-year overall survival rate of 99% with complete resection), since the 1980s, there has been a growing interest in managing recurrent, unresectable or progressive LGG with certain chemotherapeutic regimens, such as TPCV (thioguanine, procarbazine, CCNU and vincristine), carboplatin and vincristine, or vinblastine alone (40-42). The chemotherapeutic management of LGG is especially crucial for paediatric patients suffering from NF-1 (neurofibromatosis type-1), where they are both at a higher risk of developing a secondary malignancy and LGG, where the latter is usually developed within the optic tract (41). Depending on the chemotherapeutic regimen, these regimens achieve between 50-80% 3-year progression-free

survival (PFS), however, regimens like TPCV increase risks of infertility and secondary malignancies, which can be mitigated by using the carboplatin and vincristine regimen, but this regimen may offer a slightly inferior PFS compared to TPCV (41, 43).

3.3. Mechanism of action of common classes of anti-cancer drugs

3.3.1. Alkylating agents

Alkylating agents are the most common chemotherapeutic drugs used and significantly contribute to the concept of "combination chemotherapy" (44, 45). These compounds react with neutrophilic (electron-rich) moieties within cells, forming covalent bonds between these moieties and an alkyl group (44, 46). Chemically, there are two distinct groups of alkylating agents: those that react directly with biological molecules within cells (SN1) or those that form a reactive intermediate, which then reacts with biological molecules within cells (SN2) (46). The terms "SN1" and "SN2" refer to the kinetics of their reactions, where the rate of reaction for SN1 is dependant only on the concentration of the reactive intermediate and the rate of reaction for SN2 is dependent on the concentrations of the alkylating agent and the biological molecule it is reacting with (46). Examples of SN1 agents include nitrogen mustards (cyclophosphamide, ifosfamide, chlorambucil and melphalan) and nitrosoureas (carmustin and lomustine), whereas busulfan is an example of a SN2 alkylating agent (46).

Although alkylating agents react with a numerous amount of biological molecules, it is general consensus amongst the scientific community that their cytotoxic properties are due to their reaction with the DNA of biological molecules (46). The observations noted from these three early studies (47-49) helped pave the understanding of the cytotoxic mechanism of alkylating agents, suggesting that the interstrand cross-linking of DNA was the most probable mechanism of action for bifunctional alkylating agents (46). Alkylating agents are nonspecific cell-cycle agents that target DNA at any period of the cell cycle by adding a chain of carbon atoms to it, where this extra chain of carbon atoms impairs replication and repair of the DNA, breaking the long strand of DNA (50). Thus, the function of these chemotherapeutic agents is to permanently attach to the DNA at multiple locations along the DNA molecule, interfering with the tumour cell's normal functions, resulting in either a halt to cell reproduction or in programmed cell death (apoptosis) (50). Although bifunctional alkylating agents (adding two alkyl groups to biological molecules) are more efficacious anti-cancer agents than monofunctional alkylating agents, the addition of more than two alkyl groups does not further increase the cytotoxic properties of alkylating agents (46). Whilst alkylating agents are able to react with most nitrogens within DNA bases, alkylating agents display "selectivity", which is determined by the electron density of the nitrogens and the local structure of the DNA (46). Some examples of this phenomenon include: nitrogen mustards reacting more willingly with the N-7

position of guanylic acid (51), the nitrosoureas initially alkylating the O-6 position of guanylic acid (52, 53) and some monofunctional alkylating agents (dacarbazine, methylnitrosourea and procarbazine) induce methylation of the DNA, which usually occurs on the N-7 and O-6 position of guanylic acid (46).

Unfortunately, neoplastic resistance against alkylating agents has been associated to the expression of the enzyme, O6-MethylguanineDNAmethyltransferase (MGMT), where this enzyme can repair DNA injury induced by alkylating agents (50). However, drugs that inhibit MGMT may be combined with alkylating agents for children and young people with cancer to overcome the neoplastic resistance and improve the efficacy of these chemotherapeutic drugs (50). Although MGMT can be advantageous for normal cells, tumour cells are able to express this protein, rendering many alkylating agents ineffective (50). Moreover, alkylating agents have been known to cause secondary cancers, such as AML that can potentially present years after anti-cancer treatment (50).

3.3.1.1. Platinum anti-cancer agents

Platinum anti-cancer agents are platinum complexes with ligands capable of being displaced by nucleophilic atoms to create strong covalent bonds, where they share similarities with alkylating agents in the sense that they form strong chemical bonds with amino nitrogens and thiol sulfurs in proteins and nucleic acids (46). An example of a commonly used platinum anti-cancer agent is cisplatin, where the first use of cisplatin in clinical trials was in 1970s and was found to have significant anti-cancer properties against many cancers (46). Due to cisplatin's efficacy with multiple types of cancers, it became the most used anti-cancer agent, however, the nephrotoxicity and the neurotoxicity that ensued with cisplatin use led the scientific community to develop analogues to mitigate these toxicities, leading to the production of carboplatin (46). Carboplatin can lead to primary haemopoietic toxicity, but does have a similar anti-cancer effect to cisplatin (46), providing patients with more options for their chemotherapy.

3.4. Risks associated with cancer chemotherapy

Chemotherapeutic drugs do not come without side-effects and adverse events, where an adverse drug reaction (ADR) can be defined as "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (54). Furthermore, this definition of ADRs has included reactions happening because of human error, abuse/misuse, and to suspected reactions to medicinal products for unlicensed and off-label use, as well as authorised use of drugs within their normal doses (55). Due to the chemotherapeutic drugs acting on both cancer cells and normal cells,

these drugs can cause a wide range of short- and long-term side-effects (56). The side-effects and adverse events of chemotherapeutic drugs will be further discussed in the sections below.

3.4.1. Immune suppression

Many chemotherapeutic drugs can cause immunosuppression as a side-effect, whilst some of these drugs, such as cyclophosphamide (57) and methotrexate (58), are purposefully used as immunosuppressants to treat severe systemic autoimmune conditions, by impairing the proliferative or effective functions of peripheral T cells (59). Certain TKIs, such as imatinib, may also impact the adaptive immune system's T-cell arm (59), where at high dosages, imatinib blocks signalling pathways through KIT, c-ABL and BCR-ABL, which in turn suppresses T-cell proliferation and activation, where it is normally perceived to occur through LCK protein tyrosine kinase inhibition (59, 60). There is evidence (carried out on mouse models) revealing imatinib to selectively curtail expansion of memory cytotoxic T lymphocytes, without impairing primary T- and B-cell responses (59, 60). Childhood leukaemia patients undergoing treatment with imatinib may experience increase susceptibility to viral and bacterial infections due to suppression of graft-versus-leukaemia effect from allogenic transplantations (59, 61).

Immunosuppression can occur from the sudden death of many dying tumour cells through isolated limb perfusion (ILP) of chemotherapy, which causes these cells to release pro-inflammatory cytokines (such as IL-1β, IL-6 and TNF-α), which can potentially lead to the promotion of tumour progression through a molecular signalling pathway involving NF-κB (59, 62). Moreover, a theoretical explanation for this immunosuppression after ILP of chemotherapy could be due to a massive release of tumour antigens from the dying tumour cells, leading to a high-dose antigen-mediated tolerance, which can ultimately debilitate mounting reactive effector T cells (59). Previous research has shown that there is a direct correlation between the amount of antigen expressed within the periphery and the degree of T-cell proliferation and the number of tolerogenic antigen-specific $CD8^+$ T-cells in the draining lymph nodes (59, 63).

High doses of cyclophosphamide can cause immunosuppression by lymphoablation and have a direct tumoricidal effect (59), however, inducing lymphopaenia therapeutically has piqued researchers' attention in the area of adoptive transfer therapy and immunisation (via vaccinations) against melanomas (59, 64). Previous research has suggested that transient lymphopaenia enhances the efficacy of these types of therapies by activating homeostatic processes and through counteraction of tumour-induced suppression, which ultimately stimulate tumour-reactive effector T cells (59).

Although not directly chemotherapeutic, glucocorticoids (steroids) are an important component of chemotherapeutic cocktails that are used in treating many cancers affecting children and young people, where these drugs are normally prescribed to combat chemotherapy-induced nausea and vomiting (CINV) (59). Glucocorticoids subdue the synthesis of pro-inflammatory cytokines (such as IL-1α, IL-1β, IFNα and IFNβ) and chemokines (such as CXCL8, CCL7, CCL8, CCL13, CCL17, CCL19 and CCL20) through the healthy donors' blood mononuclear cells (59, 65). Whilst glucocorticoids induce expression of pattern-recognition receptors, such as TLR2 and TLR4 (which lead to an innate immune response), studies have shown that these drugs also gravely impair the antigen presentation and differentiation of dendritic cells in vitro and in vivo (59, 66). Furthermore, previous evidence has shown that glucocorticoids repress expression of genes that are associated with the adaptive immune response, amend T-cell function and development, stifle the development of T_H1 cells and promote bias responses toward the T_H2-cell type, therefore preventing the elicitation of memory and effector anti-tumour immunity (59). Moreover, many members of the TGFβ family (which suppress natural killer and T-cell effector functions) undergo glucocorticoid upregulation, where these drugs subdue cell-surface expression of NKp30 and NKp44 (the main natural cytotoxicity receptors) and impair the IL-2 and IL-15-triggered natural killer cell proliferation, whilst detrimentally affecting the natural killer cell cytotoxicity, which is mediated by NKp46, 2B4 or NKG2D (59).

3.4.1.1. Common infections within paediatric oncology

Infections are a major cause of morbidity and death in paediatric cancer patients, where infectious complications have long been considered a limiting factor in cancer therapy (67-72). The risk of infection increases during chemotherapy as there is bone marrow suppression and therefore, immune suppression (67). During the last 20 years, the predominance of organisms cultured from paediatric patients with cancer has changed from gram-negative organisms to gram-positive and fungal organisms (67, 70, 73-77). These findings have largely been attributed to more intensive chemotherapy regimens causing profound neutropenia (67, 78, 79) and an increased use of central venous catheters (70, 80, 81).

A study reviewed medical records of 155 paediatric patients with cancer to identify the distribution of infections amongst this population, where 330 infections were identified, including 19 polymicrobial infections recorded for 85 patients, with 310 infections having a known correlative neutropenic status (67). Out of this population, blood infections (n=70), otitis media (n=70) and UTIs (n=29) were the most prevalent infections noted (67). Most infections of this population followed a bimodal distribution across four age groups: 129 (39%) infections in patients younger than 3 years; 76 (23%) infections in the group of 3-6 years old; 30 (9%) infections in the group older than 12 years. Infections were generally more prevalent amongst boys, except for UTIs, where there was a female

predominance (n=22, 76%) (67). 64% of patients (n=197) of infections occurred in the 51 patients with leukaemia/lymphoma and 36% (n=113) of infections occurred in the 51 patients with solid tumours. Comparing the leukaemia/lymphoma group and the solid tumours group, the most prevalent infection within the former group were blood infections and otitis media, whereas the most prevalent infection within the latter group were blood infections, otitis media and UTIs (67). However, more infections occurred during the remission disease (n=209) than during the active disease (n=175), whilst most infections (n=175) occurred in the absence of neutropenia (67).

3.4.1.2. Acute Kidney Injury and chemotherapeutic drugs

Children and young people with cancer may experience acute kidney injury (AKI) as an adverse effect of the treatment and/or the course of their disease (82). Whilst AKI can occur due to the cancer itself, through tumour lysis syndrome (TLS) and direct infiltration of the genitourinary system by neoplastic cells, AKI can also occur through the use of nephrotoxic drugs, with chemotherapeutic drugs being a major class within this group (82-85). Moreover, AKI is associated with prolonged hospital admission and a decreased survival, thus incurring a more negative prognosis of disease (82). As AKI occurs in children and young people with cancer, being one of the major causes of morbidity and mortality amongst cancer patients, treatment agents may be required to be altered or removed entirely from the treatment plan and adequate assessment of baseline renal function before initiation and during therapy is crucial for the optimisation of dealing with chemotherapy-induced AKI amongst children and young people (86).

Additionally, children and young people with cancer are often treated with nephrotoxic antibiotics such as vancomycin, amphotericin B and aminoglycosides for difficult-to-treat bacterial and fungal infections (86), where these patients may also undergo other nephrotoxic therapies to treat or diagnose their malignancy, such as radiation therapy and iodine contrast media for their radiological studies (86-88). Furthermore, risk factors such as pre-existing renal insufficiency, diabetes mellitus, the use of other nephrotoxic drugs (e.g., NSAIDs and allopurinol) and extracellular volume depletion have the potential to potentiate chemotherapy-induced nephrotoxicity (86, 89, 90).

3.4.1.2.1. Incidence of chemotherapy-induced AKI in children and young people

Although the incidence of AKI amongst cancer patients has been adequately investigated, there is a considerably lower amount of data regarding AKI incidence amongst children and young people with cancer (82). Previous research shows that the incidence of AKI amongst children and young people with cancer is between 11% and 84%, however most of these studies are limited to patients with haematological malignancies (82, 91-93). One study had a total of 2170 paediatric patients with cancer that suffered from a wide range of malignancies, where 983 patients (52.6%) developed AKI and had a total of 1864 AKI episodes within their first year after diagnosis of their disease (82). This

study also reported that 293 patients (15.7%) presented with AKI at diagnosis (high serum creatinine at presentation) and identified the median onset of first episode of AKI after cancer diagnosis within their population group to be 9 days (82). Furthermore, the study identified correlations between the 2-week and 1-year cumulative incidences of AKI and different malignancies, where they reported the 2-week cumulative incidence to be highest in ALL (58.5%) followed by AML (45.2%) and medulloblastoma (45.0%), and the 1-year cumulative incidence to be highest in AML (88.4%) followed by ALL (77.2%) (82). Chemotherapy-induced renal injury can lead to tubular and glomerular dysfunction (86, 94, 95), where AKI, renal capillary endothelial injury, tubulointerstitial disease and acid-base disorders are the most common adverse effects of chemotherapy amongst children and young people with cancer (86, 96).

3.4.1.2.2. Cisplatin-induced AKI

Although having a relatively high cure rate of some paediatric cancers (90%), the presentation of AKI occurs in 20-80% of children and young people with cancer treated with cisplatin, where AKI is an adverse effect that can limit the tolerable dose levels of cisplatin (97-101). Cisplatin acts on the S3 segment of the proximal tubule, where the nephrotoxicity of cisplatin usually presents with a decreased GFR and an increased serum creatinine, along with hypokalaemia and hypomagnesemia (97, 101-104). The nephrotoxicity of cisplatin is typically persistent amongst children and young people with cancer (102, 105), where risk factors include dehydration, hypoalbuminemia concomitant use of other nephrotoxic drugs and cumulative dose (97). Treatment for cisplatin-induced AKI includes supportive care for the AKI, where magnesium supplementation should be provided for individuals with hypomagnesaemia (97, 106).

A study revealing the mechanism of cisplatin-induced renal injury notes that cisplatin is taken up by basolateral OCT2, which results in the synthesis of ROS (whilst activating signalling pathways), MAPK, P53 and potentially P21, which ultimately leads to renal tubular cell death (97, 99). Furthermore, an inflammatory process occurs, plausibly due to the activation of TNF-α receptor 2 by the intrinsic production of TNF-α (97). For some of these changes, oxidative stress seems to be both a driving force and an end result (97, 99, 107).

As targets responsible for cisplatin-induced renal injury have been identified, this has allowed the evaluation of several compounds that can assist to counteract the cisplatin-induced nephrotoxicity (97). Examples of drugs that have been evaluated to counteract cisplatin-induced nephrotoxicity are erythropoietin (blocking apoptosis), quercetin (prevention of inflammation) and cimetidine (prevention of renal transport of cisplatin and prevention accumulation of cisplatin) (97, 99, 107). Nevertheless, these drugs do not target the most exploitable mechanism of prevention of cisplatin-induced nephrotoxicity, which happens to oxidative stress (97), where several antioxidants such as

NAC, theophylline, amifostine and sodium thiosulfate have been evaluated to deter the effects of oxidative stress caused by cisplatin (97, 108-112). However, only amifostine and theophylline have been assessed in RCTs, with amifostine showing positive results (reducing nephrotoxicity from 30% to 10%) in a trial of women suffering with ovarian cancer, but not doing positively in a trial assessing cisplatin-induced nephrotoxicity amongst children with osteosarcoma (97, 109, 110). Although theophylline has not been assessed in RCTs, previous studies have shown that theophylline has had mixed results, with positive findings in some trials and negative findings in others (97, 112, 113).

3.4.1.3. Common short-term side-effects of chemotherapy agents

3.4.1.3.1. Gastrointestinal side-effects of chemotherapeutic drugs

Although chemotherapeutic drugs have greatly improved the survival rates of paediatric patients with cancer, there are many side-effects associated with their use, with many of its most common being gastrointestinal side-effects (114). Side-effects such as; diarrhoea, vomiting, nausea and hepatoxicity can often lead to dose reduction, discontinuation of treatment, significant morbidity or even mortality (114, 115). Gastrointestinal side-effects can also significantly impact performance status, which can lead to social isolation, psychological distress and in some cases, reluctance to continue treatment (114, 115). Some gastrointestinal side-effects, such as constipation and chemotherapy-induced diarrhoea, may persist many years after treatment (114).

Chemotherapy-induced diarrhoea can be debilitating and potentially life-threatening, particularly when it presents with neutropenia (115, 116). Acute chemotherapy-induce diarrhoea is particularly associated with 5-fluoruracil (5-FU), tyrosine kinase inhibitors (TKIs) and irinotecan-based regimens (116). Chemotherapeutic drugs can also cause mucositis, an inflammatory response of the mucous membranes within the alimentary tract (117). Mucositis can present as oral mucositis and gastrointestinal mucositis (117). There is no treatment for gastrointestinal mucositis, with supportive care being the mainstay of treatment of gastrointestinal mucositis (117). Moreover, research regarding mucositis has been focused on oral mucositis and gastrointestinal mucositis in adults, thus identifying the need to fill this gap of knowledge based on the scarcity of paediatric data on gastrointestinal mucositis (117). Considering there is no gold standard with diagnosing gastrointestinal mucositis, there has been no consistency within the methods to ascertain the frequency of gastrointestinal mucositis (117). In one study observing nine children with acute myeloid leukaemia, gastrointestinal mucositis was experienced in 55% of the chemotherapy cycles, whilst in another study observing a heterogenous group of 15 children with cancer, 28% of the children experienced gastrointestinal mucositis during their chemotherapy cycles (117-119). The clinical presentation of gastrointestinal mucositis is probably similar for adults and children, with several factors likely to be involved: altered fluid transport, an altered gut motility with consequently

decreased transit time and reduced water absorption, changes to the microbiota and fermentation (117, 120, 121).

Paediatric cancer patients frequently experience gastrointestinal/liver dysfunction due to a variety of risk factors, including abdominal surgery, mechanical obstruction by tumour mass, neoplastic infiltration, radiation therapy, and, most significantly, antineoplastic treatment, which has a variety of effects depending on the dose, drugs prescribed, schedule and associated treatments (122). Systemic chemotherapeutic therapy may result in direct damage to the gastrointestinal and hepatic tissues, as well as immunosuppression and nutritional impairment (122). Therefore, paediatric patients with cancer are more prone to developing liver and gastrointestinal infections that may have a detrimental effect of their morbidity and mortality (122). Gastrointestinal infections may present with non-specific signs and symptoms in children undergoing chemotherapy, where these include; haemorrhage, abdominal pain, with or without fever (122). Although gastrointestinal haemorrhage is not a frequent clinical condition in paediatric oncology, it can potentially life-threatening in paediatric cancer patients with thrombocytopaenia (122). With regards to gastrointestinal haemorrhage, fever is generally absent and neutropenia can be frequently but not consistently detected (122).

3.4.2. Drugs used for side-effect management of paediatric oncology

In addition to requiring medication to treat the underlying malignancy, patients receiving anti-cancer chemotherapy will usually experience adverse effects related to their treatment. The most common clinically significant adverse drug reactions that require treatments are as follows:

3.4.2.1. Infection

Most forms of anti-cancer treatment can affect the patient's immune system, which can make it more likely to develop an infection (123). Certain chemotherapeutic drugs can affect bone marrow activity (myelosuppression) which leads to decrease of white blood cells (neutropaenia) and whilst children and young people are on these drugs, doctors will specifically monitor levels of neutrophils, as neutropaenia leaves the patient more vulnerable to bacterial infections that they may not be able to fend off themselves (123, 124). Febrile neutropaenia (FN) is a term used to denote the clinical presentation of myelosuppressed patients with fever, however, there is a wide range of temperature triggers and neutrophil thresholds that have been utilised to identify episodes of FN (125, 126). Whilst chemotherapeutic drugs have the potential to produce neutropaenia, immunotherapeutic drugs work by using cytokines, which are also naturally produced by the body to help regulate and instruct the immune system toward an infection, where these cytokines have some accountability for some of the symptoms of an infection, such as fever (123). Immunotherapy results in increased

levels of circulating cytokines, which is one of the reasons why these agents might cause symptoms such as fever (123).

NICE recommends treating suspected FN as an acute medical emergency and offer all patients with piperacillin/tazobactam immediately, unless there are local microbiological or patient-specific contraindications (127). However, at the time NICE released this guidance (September 2012), piperacillin/tazobactam did not have a UK marketing authorisation for use in children under the age of 2 years old (127). The prescriber should follow relevant professional guidance, taking full responsibility for their decision (127). Furthermore, NICE recommends to not change initial empiric antibiotics prescribed in patients with unresponsive fever and only discontinue treatment once the FN has responded to treatment (irrespective of neutrophil count) or there are signs of clinical deterioration and other microbiological indications (127).

3.4.2.2. Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) are very common adverse effects of cancer treatment for children and young people (128). These adverse consequences are the result of the body's efforts to eliminate harmful chemicals from the stomach and intestines (128). Vomiting (also called emesis) is regulated by the emesis centre, which is situated in the medulla. This centre takes input from the chemoreceptor trigger zone (CTZ), which possesses several 5HT3 (serotonin) receptors, NK1 (norepinephrine) receptors, and D2 (dopamine) receptors (128). CINV can be grouped into 4 stages, which are dependent on the time of onset (128, 129). The acute stage is 0-24 hours after 1st dose of chemotherapy, the delayed stage is 24 hours to 5 days post chemotherapy, the anticipatory stage occurs with patients prior to the start of chemotherapy (normally having a history of conditions relating to nausea and vomiting) (128). The last stage of CINV is the breakthrough stage is when the patient experiences CINV despite appropriate antiemetic prophylaxis (129).

With regards to the management of CINV amongst children and young people, common drugs used to treat CINV for this population group are ondansetron, aprepitant, dexamethasone, metoclopramide, levomepromazine, lorazepam and nabilone (129). Drugs like ondansetron are 5-HT_3 (serotonin) receptor antagonists, which are regarded as the “gold standard” in the treatment of CINV, however when concerning delayed CINV, ondansetron is less efficacious than metoclopramide (129). Moreover, for delayed CINV, dexamethasone is particularly effective at treating this type of CINV, especially when combined with other antiemetic drugs, such as metoclopramide and ondansetron (129). Drugs like lorazepam and nabilone are used less commonly due to their minimal anti-emetic effects and non-availability of formulations other than a capsule, respectively (129).

3.5. Infections and paediatric oncology

3.5.1. Incidence density and duration of treatment of infections within paediatric oncology

3.5.1.1. Healthcare-associated infections and bloodstream infections

Patients undergoing chemotherapy in paediatric oncology have a greatly increased risk of possibly fatal infectious consequences (130-134) due to their underlying oncological disease and the immune suppression caused by their anticancer treatment (130, 134). Most of these infections are bloodstream infections (BSIs), where many of these infections are greatly associated with central venous access devices (CVADs) (130, 134).

Two single-centre prospective studies investigating the healthcare-associated infections (HAIs) in paediatric oncology patients found an incidence of HAIs amongst 20% of their patients (10.8 HAIs/1000 inpatient days) (135) and 24% of their patients (17.7 HAIs/1000 inpatient days) (136) , respectively . Another study found that incidence of HAIs amongst patients from a paediatric stem-cell and bone-marrow transplantation unit to be 38.9 HAIs/1000 inpatient days, however, it was emphasised that the relevant procedure applied solely to children with neutropaenia (130, 134) . In 2008, a German group published the results of a multicentre prospective surveillance study for HAIs and nosocomial fever of unknown origin (nFUO) that encompassed 7 German paediatric oncology centres from 2001 through 2015, where out of 54,824 surveyed inpatient days, 727 HAIs and nFUOs were documented amongst 411 patients (134). Of these recorded HAIs and nFUOs, 263 (36%) were HAIs, resulting in an incidence density (ID) of 4.8 HAIs/1000 inpatient days. Of the 263 HAIs, 153 (58%) were BSIs, and out of the BSIs, 89% of the BSIs were associated with the use of a long-term CVAD, which ultimately led to an overall ID of 2.8 BSIs/1000 utilisation days (134). This value was significantly lower with the use of Port-type than in Hickman-type CVADs (134).

Only one study investigated BSI data amongst a single paediatric haematology/oncology centre, that also included data regarding the duration of inpatient treatment of BSIs amongst a paediatric oncology population. This study reports that patients with gram-negative microorganisms were usually treated for 2 weeks and gram-positive BSIs were normally treated for 10 days, where all patients were followed up for at least 6 months (132).

3.5.2. Most common bacteria found in febrile neutropaenia amongst a paediatric oncology population

Many community-acquired pathogens can cause FN, however, opportunistic infections should also be considered (133). The most common pathogens causing FN are bacteria, but both viruses and fungi are relatively common causes of FN, where fungal infections should be strongly considered in prolonged FN (133). When attempts to identify microbiological causes for suspected FN fail and

patients fail to improve on antimicrobial treatment, non-infectious causes of fever should be considered (133).

The most common type of pathogens causing FN are Gram-positive cocci, particularly skin commensals resulting from an increased use of prophylactic antibiotics and central venous lines (133). Coagulase-negative Staphylococci (especially *Staphylococcus epidermis*), *Staphylococcus aureus* and Streptococcal species make up 50-67% of causative organisms found within microbiological cultures in samples tested for suspected FN (133). Due to the increasing use of fluoroquinolone prophylaxis, rates of selective resistance have significantly increased largely because of selective intestinal pressure (133).

Whilst Gram-negative organisms are less common causative agents of FN, they may lead to a more fulminant clinical course due to the endotoxins produced and other virulence factors (133). Examples of common causative gram-negative bacteria of FN are *Pseudomonas aeruginosa*, *Eschericia coli* and the members of the klebsiella species, where polymicrobial infections are common with this group of bacteria (133).

3.5.3. Doses and routes of antibiotics required to treat febrile neutropaenia

Treatment of FN is based on a variety of factors, including patient symptoms, previous cultures and sensitivities (for both infecting and colonising organisms) and regional resistance patterns (133). Broad spectrum antibiotics are the first line treatment for FN, which ensures the coverage of both gram-positive and gram-negative bacteria (127, 133). Although a cocktail of antibiotics can improve efficacy of treatment, monotherapy with a broad-spectrum antibiotic has been demonstrated to lower mortality and have fewer adverse effects than two or more antibiotics (133).

3.5.3.1. Doses

Beta-lactam antibiotics, where a prime example for the case of FN would be piperacillin-tazobactam, are recommended by NICE to be provided empirically as the “first line monotherapy, unless there are previous microbiological results which indicate a resistant organism” (133). NICE recommends a dosage of 90mg/kg/dose every six hours of piperacillin-tazobactam for FN, with a maximum dose of 4.5mg per dose (127, 133). According to the British National Formulary for Children (BNFC), treatment recommendations for FN are also made for imipenem with cilastatin (25 mg/kg every 6 hours, with a maximum dose of 1g per dose) (137) and ceftazidime (50mg/kg every 8 hours, with a maximum dose of 6g per day) (138). Due to the likelihood of cross-reaction, individuals with risk of allergy to penicillin should not be provided cephalosporins or carbapenems (133); instead, these patients should be provided alternative broad-spectrum antibiotics, such as ciprofloxacin with a glycopeptide (vancomycin or teicoplanin) (133).

3.5.3.2. Routes

Although FN can be treated on an outpatient basis, all patients that are deemed as high-risk for FN should be treated as inpatients, where patients will only be considered for outpatient treatment when they have increasing neutrophil counts, stable renal and hepatic functions, no significant comorbidities, and their FN is not expected to last longer than 7 days (133). These patients must also have adequate gastrointestinal absorption, have had a course of IV therapy for FN (within 48-72 hours of onset) and must not be receiving fluoroquinolone prophylaxis prior to the FN episode (133). One of the most common empiric regimens for the outpatient management of FN is oral ciprofloxacin with amoxicillin-clavunate (can be substituted to clindamycin if patient has a penicillin allergy) (133). When concerning inpatient treatment, the doses of the drugs used are listed above, where the preferred route of the administration of these drugs is IV (133).

3.6. OPAT, elastomeric devices and paediatric oncology

3.6.1. Quality of life of paediatric oncology patients managed as inpatients

Although treatment advancements of paediatric cancers have improved significantly over the last few decades, leading to increased prospects of surviving childhood cancer, childhood cancer is likely to perpetuate itself through the stresses faced by paediatric oncology patients and their families alike (139). The WHO (World Health Organisation) defines health as "the state of complete physical, mental, and social well-being, not merely the absence of disease or infirmity" (140), which highlights the importance of understanding the emotional and social dimension of health in addition to physical health, when concerning paediatric oncology patients.

It is well known that cancer and its treatment can predispose paediatric oncology patients to late morbidities, such as organ damage, infertility, cognitive impairment, alterations in growth and development and secondary malignancies (139, 141). Treatment-related complications such as cardiopulmonary toxicity, neuro-cognitive dysfunction and endocrinopathies can cause a serious impact on the functioning of both patients and survivors of childhood cancer (139). Both adverse consequences on parent's/caregiver's immediate physical and mental health and an increased incidence of depression and anxiety have been reported amongst paediatric oncology patients undergoing treatment (139, 142-145). Despite the facts regarding the negative impacts of cancer treatment, the current aggressive treatment regimens invoke concerns and awareness for the quality of life for those undergoing treatment for cancer (139). Considering one of the most common childhood cancers, ALL, contemporary chemotherapy regimens for this disease are somewhat lengthy, with medications administered over 2.5-3.5 years, thus adding further rationale for the understanding of the quality of life for these patients (146). Various scales to measure healthcare-related quality of life (HRQoL) in paediatric oncology patients have been developed (147-149), where

many international studies show that paediatric oncology patients during the acute phase of their disease show a reduced QoL (150-156).

A study performed amongst a group of 75 paediatric oncology patients in India (139) verifies the burden of cancer to QoL, with 3 scales (Lansky, HUI-2 and WHO QOL BREF) being significantly poorer in the paediatric oncology group compared to their controls, whilst showing significant improvement in their QoL after therapy for patients suffering from lymphomas and miscellaneous tumours. However, one study (150) that assessed the QoL of 56 newly diagnosed paediatric oncology patients in Greece showed that the QoL of children and adolescents did not change significantly during their treatment, where children and adolescents diagnosed with haematological cancer, teenage patients and male patients scored higher QoL scores than other population groups within their study.

3.6.2. Outpatient management of low-risk febrile neutropaenia

Although FN is a potentially deadly consequence of cancer therapy (requiring prompt, empirical therapy), individuals with FN are a diverse population, with only a small proportion developing major medical complications (157-159). To identify low-risk FN patients, scoring methods such as the Multinational Association for Supportive Care in Cancer (MASCC) have been created and validated. (157, 160), furthermore, the use of ambulatory, outpatient management of patients with low-risk FN has proven to be cost-effective and safe (161), with two meta-analyses demonstrating the utility of this approach, with Cartensen et al. (162) examining 10 studies that compared inpatient and outpatient therapy of FN (which did not find any significant difference in mortality or outcome) and Teuffel et al. (163) examining 14 randomised studies that assessed outpatient management of low-risk FN, where they concluded that it was a safe and efficacious strategy in the treatment for the respective cohorts of patients included within the studies (157).

Ambulatory care encompasses most of traditional hospital care, including diagnostics and treatment (157). However, a key feature of ambulatory care is that patients are not admitted, which provides patients an opportunity to spend most of their time away from the hospital. Ambulatory care differs from outpatient care due to its focus on caring for acutely unwell medical patients and facilitating discharge from patients who would ordinarily stay in the hospital (157). Thus, to function successfully, ambulatory care units are staffed by a multidisciplinary team with close links to other acute services, especially the acute medical unit (AMU) (157). The benefits of ambulatory care are both numerous and well-known to acute physicians, where they include cost savings, admission avoidance, improved patient experience and satisfaction, and a reduced risk of nosocomial infections (157).

A study that measured parents' and healthcare professionals' preferences with regards to inpatient versus outpatient management of low-risk paediatric FN reported no significant difference between the proportion of parents and healthcare professionals who would choose outpatient management (164). Additionally, this research discovered that a parent's preference for oral outpatient treatment was related with a greater predicted quality of life for the parent and child at home than in the hospital, a higher priority rank for "comfort," and a lower importance rank for "fear/anxiety" (164). In contrast, only a lower priority rank for "fear/anxiety" was related with a higher preference score for outpatient oral antibiotic therapy in professionals (164).

3.6.3. The use of elastomeric pumps within paediatric oncology

Historically, home chemotherapy involved administering the treatment under the supervision of a specially trained nurse (165). Elastomeric pumps are one form of medical equipment used for drug infusion. They enable patients to receive prolonged infusions safely and independently, with community nurses visiting the patient to disconnect the device at the conclusion of the infusion (165). Patients prefer chemotherapy administered using elastomeric devices because they may be attached in the hospital/cancer centre and then return home to receive visits from the community nursing team, which minimises disturbance for families and caregivers alike (165).

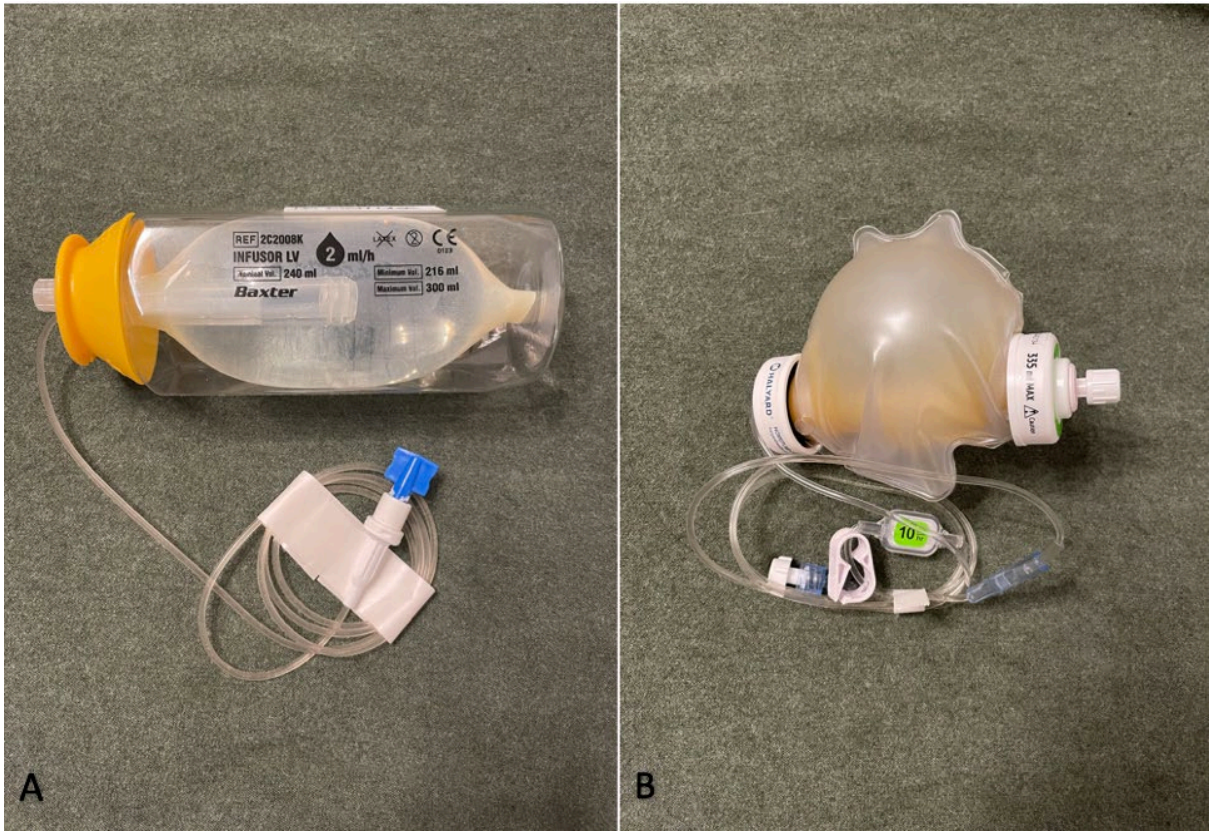
Despite its benefits, chemotherapeutic drug delivery using elastomeric devices has several drawbacks. As home chemotherapy services became more popular, nurses originally expressed worry about a previously unknown hazard with these devices (165). When the nurses arrived to disconnect the elastomeric pumps at the specified time, they discovered that not all pumps had completed the chemotherapy volume infusion (165). The nurse has two alternatives in such situations: disconnect and discard the pump or allow the pump to continue infusing (165). While the first method adheres to the established procedure, it results in patients getting less than the recommended dosage (165). In comparison, the second technique allows for the complete dosage to be injected but results in greater patient wait times or schedule disruptions for district/community nurses who must return later to disconnect the patient (165). Variation in home chemotherapy administration with elastomeric pumps was anticipated but not empirically quantified (165). As a result, the authors originally chose to undertake four laboratory tests (166) to determine the accuracy of flow rate and end of infusion duration of several commercially available elastomeric pumps (165). Temperatures of the flow controller and the actual elastic reservoir, as well as the viscosity of the diluent, were considered (165). The experiment was straightforward: temperatures and viscosity were changed, and the devices' performance was observed (165). The observed flow rate did not match the prescribed flow rate, and it fluctuated according on the temperature and diluent viscosity (165). The temperature surrounding the pump, on the other hand, varies

dramatically across users and over the infusion period (165). This temperature variation will introduce further irregularities, not only in the pump flow rates, but also in the chemotherapeutic regimen's stability (165).

4. Systematic review of elastomeric devices

As previously discussed, infections are a common part of paediatric oncology and patients require numerous inpatient stays for their management. Elastomeric devices may be able to be useful within this population, but the evidence is not yet clear. Therefore, the aim of this review is to identify which antibiotics have been evaluated for use in elastomeric devices amongst a paediatric population, and report on the range of paediatric infections that have been treated, the efficacy of treatment, reported adverse effects, and pharmacokinetic data, to identify areas where the use of such devices is supported, and where evidence is lacking. ***Figure 1*** shows two examples of common elastomeric devices used in the UK, obtained from Alder Hey's Children Hospital.

Figure 1. Two of the most common elastomeric devices used in the UK (acquired from the pharmacy at the Alder Hey Children's Hospital)



(A) Baxter Infusor LV 2

(B) Halyard HOMEPUMP C-SERIES

4.1. Methods

4.1.1. Study design and setting

To undertake a systematic review of studies that assessed antibiotics delivered through elastomeric devices within the paediatric population (defined as children, young people or paediatric patients aged from 0 to 21 years old) was conducted, using PRISMA methodology (167).

4.1.2. Information sources and search strategy

Electronic databases, CINAHL, EMBASE, MEDLINE and PubMed were searched up to November 2020 to identify relevant studies. The search terms were based upon 3 main terms: “paediatric”, “elastomeric device” and “antibiotic”. There were no date or language restrictions.

4.1.3. Inclusion criteria and study selection

There are no restrictions on the type of study design for included studies, however, studies must be clinical with at least one paediatric patient having been delivered antibiotics through an elastomeric device. Furthermore, studies included must display the name of the antibiotic delivered through the elastomeric device. Although elastomeric devices and OPAT are heavily synonymous, studies concerning both inpatient and outpatient use of elastomeric devices have been included. Studies regarding wider schemes and therapies such as OPAT and HITH (Hospital in the Home) which involve multiple delivery mechanisms but in which it is not possible to extract the elastomeric device data separately were excluded, if authors could not be contacted and separated data provided

Studies that contain evaluable data on antibiotics delivered through an elastomeric device, in patients from 0 to 21 years of age, were included. Exclusion criteria were studies that only included adult data (>21 years old), or in which the adult and paediatric data were not separatable, conference abstracts and review articles. See supplementary data section for full inclusion and exclusion criteria. Additional papers were located through searching the references of included full-text papers to see if more studies would be eligible for inclusion.

4.1.4. Data extraction

Two reviewers (VS and JC) screened the articles for their title and abstracts. They independently screened records for inclusion, and they checked their results at the end of the title/abstract stage, had a clear discussion about their opinions and differing results, before moving on and performing the same steps to screen the included articles for their full-texts.

A data extraction tool was created and used on the full-text articles. Data was extracted by VS or a native speaker (if the language was not English). The data extraction tool included study design, study duration, gender, age-range, number of patients and/or number of individual patient episodes. In addition, data on antibiotics delivered through an elastomeric device, type of

elastomeric device, duration of treatment, most frequent diseases being treated, cost analysis, patient satisfaction, side-effect profile, amount of monitoring required, patient outcomes, pharmacokinetic and pharmacodynamic data were collected. A senior author (DH) and an author (VS) conducted the data extraction, where the author (VS) performed the data extraction, and a senior author (DH) verified the extracted data. They were both responsible for contacting the study investigators for unreported data or additional details.

4.1.5. Study outcomes

The pre-specified primary outcome of this review is the identification of names of antibiotics administered through elastomeric devices, within a paediatric population. The secondary outcome is to use additional evaluable data contained within included articles to support or oppose the evaluation of the antibiotics in question. Some of the data categories that compromise of "evaluable data" include the age range of the study population, number of patients within the study, most frequent diseases being treated, percentage of positive microbiological cultures and their source, complications associated with elastomeric devices, the side-effect profile of antibiotics administered through these devices, drug monitoring required and patient outcome data relating to elastomeric devices. Collated data is summarised into individual sections to allow readers and clinicians to view the evaluation of the use of antibiotics delivered through elastomeric devices within a paediatric population.

4.2. Results

A total of 320 articles were identified through electronic database searching (CINAHL, EMBASE, Medline, PubMed), with two articles being identified through additional sources. After removing duplicates, 243 articles had their titles and abstract screened, and 53 were eligible for full-text screening. Of the 53 articles, 50 were excluded, resulting in three studies included for the qualitative synthesis of this review. Data from one study was received from the authors, enabling us to produce elastomeric data separately, when this is not directly possible from the original manuscript itself. A summary of the included articles is shown in ***Table 1***.

Table 1. Summary of studies included in the systematic review

Type of elastomeric device used	Antibiotics delivered through elastomeric devices (n, %)	No. of patients	Mean age in years (range)	Median duration of treatment in days (range)	Diseases being treated (n, %)	Ref
Eclipse C series 1-day pump and the Baxter LV10 System. 9 patients (18%) were reported with no pump specific data	Piperacillin-tazobactam (n=18, 53%), flucloxacillin (n=9, 26%) and ceftazidime (n=5, 15%)	34	10.4 (7 months to 18 years old)	10 (2-84)	Infective exacerbations of cystic fibrosis (n=11, 32%), infective endocarditis (n=5, 15%), osteoarticular infections (n=4, 12%), surgical site infections (n=3, 9%) and complex intra-abdominal infections (n=2, 6%)	(168)
Baxter Intermate SV 200 portable and the Baxter Infusor LV10 portable device	Ceftazidime (n=49, 100%), tobramycin (n=49, 100%) and ciprofloxacin (n=30, 61.2%)	49, male/female ratio was not provided	23.3 ± 5.2*, age range was not provided	Median duration of treatment not provided (14-21)	Infective exacerbations of cystic fibrosis (n=49, 100%)	(169)
Baxter Intermate 100/200 and the LogoMed home pump (Eclipse)	Ceftazidime (n=7, 100%), gentamicin (n=2, 28.6%), tobramycin (n=2, 28.6%) and amikacin (n=3, 42.9%)	7, male/female ratio was not provided	10.7 (5 to 20 years old)	14	Infective exacerbations of cystic fibrosis (n=7, 100%)	(170)

*Although the mean age of the 2nd paper is larger than the age range detailed in our inclusion criteria, the standard deviation allows the mean age to intersect with the age range set within the inclusion criteria. Furthermore, due to the lack of data regarding this topic and that no other articles met this criterion, we have included this study within the systematic review.

4.2.1. Quality of life analysis

Within one of the studies included, all families of patients were provided with feedback questionnaires on their experience of elastomeric device use as part of their p-OPAT service, including their views on the administration of the service. 18 questionnaires were returned from this studies' cohort, with 17 families (94%) stating that they would accept OPAT as a form of treatment if the need for it arises again, with the other one family (6%) unsure whether they would prefer p-OPAT over inpatient treatment. All families agreed that p-OPAT either met or exceeded their expectations. The questionnaire provided a free text comment section for families to address any opinions or concerns about the service, where a common theme of comments was that families felt that they were able to get back to their day-to-day lives when discharged under p-OPAT, with comments like "amazing" and "robust" used to describe their experience.

Another study provided opportunities for their cohort of patients to fill in questionnaires (Cystic Fibrosis Questionnaire score of 14+ for teenagers and adults, and Cystic Fibrosis Questionnaire Child score of P for children aged 8 to 13) to obtain quality-of-life scores. According to this study, the scores were similar for both treatment regimens, however, 82% of 57 patients who received both modalities of treatment stated that they preferred the continuous infusion treatment course over the three short infusion treatment courses of ceftazidime.

4.2.2. Antibiotics delivered through elastomeric devices

Seven antibiotics (ceftazidime, tobramycin, ciprofloxacin, piperacillin-tazobactam, flucloxacillin, amikacin and gentamicin) have been evaluated for use in children and young people via elastomeric devices, in three published studies. Antibiotics delivered through elastomeric devices and their distributions (with regards to their study populations) are displayed in ***Table 1***. Out of the three studies, only one study reported the dose of antibiotics used, which was 200 mg/kg (maximum dose of 12 g) for short infusions of ceftazidime, a loading dose of 60 mg/kg (maximum dose of 2g) for continuous infusions of ceftazidime (BNFC states 50 mg/kg every 8 hours; maximum 9g per day) and 10 mg/kg for daily short infusions of tobramycin. Only one study specified how long an individual patient was in the study for, which was defined as "from when the child/patient was ambulated on OPAT until when the IV antibiotics were stopped."

4.2.3. Infections being treated

Five types of infections have been reported within the three included studies in the systematic review, where their distributions have been displayed in ***Table 1***. There are a total of 90 paediatric patients (used PP population instead of ITT population for one of the studies) amassed from the three included studies, that were treated with antibiotics delivered through an elastomeric device. Out of these 90 patients, the most common type of infection treated is exacerbation of cystic fibrosis

(n=66, 73.3%). However, only one study reports other infections compared to the two studies that only reported to treated infective exacerbations of cystic fibrosis.

4.2.4. Microorganisms identified

All three studies included within this review identified microorganisms in the patients' cultures. Out of the 90 patients within the three included studies, there were 72 patients (80%) identified with positive bacterial cultures and the organisms were; *Pseudomonas aeruginosa* (n=67, 93.1%), *Staphylococcus aureus* (n=50, 69.4%), *Haemophilus influenza* (n=9, 12.5%), *Achromobacter sp.* (n=4, 5.6%), Streptococcus sp. (n=3, 4.2%), coliforms (n=2, 2.8%), *Stenotrophomonas maltophilia* (n=2, 2.8%) and *Serratia marcescens* (n=2, 2.8%).

4.2.5. Efficacy of treatment

Only two studies explicitly reported data on the efficacy of the treatment provided. One study reported that within their case series, 26 children (76%) were cured from their infection, with six patients (18%) having "partial improvement" and two patients (6%) experiencing treatment "failure" (see ***Table 2*** for definitions of terms contained within quotation marks). With regards to the two patients that experienced treatment failure, one patient had a chronic granulomatosis disease that was initially treated for a lower respiratory tract infection with piperacillin-tazobactam but then deteriorated requiring admission and commencement of antifungal treatment, and the other patient suffered from cerebral palsy and epilepsy whom was conservatively treated for a splenic abscess caused by P. aeruginosa, where their infection persisted until a source control measure was taken (splenectomy).

Table 2. Treatment outcome definitions as defined in the study published by Patel et al.

Infection outcome			OPAT outcome (events related to IV access or antimicrobials)		
Cure	Partial improvement	Failure	Success	Partial success	Failure
Paediatric OPAT therapy was completed and/or an oral-step-down was decided for a defined duration, with resolution of infection and no requirement for long-term antibiotic therapy	Completed paediatric OPAT therapy with partial resolution of infection requiring long term oral step-down/escalation of antibiotics *or* cure requiring escalation of antibiotics (without readmission)	Progression or lack of clinical response despite paediatric OPAT, resulting in readmission, surgical intervention or death	Completed paediatric OPAT therapy with no change in antibiotics and no adverse events (due to line complications or antimicrobial side effects)	Complete therapy in paediatric OPAT with either change in Parenteral antibiotic agent or adverse event not requiring readmission (due to line complications or antimicrobial side effects)	Readmission or death due to adverse event (line complications or antimicrobial side effects)

The other study that presents data on efficacy of treatment reported that the values of FEV_1 at the beginning of the short infusions (44.4, 18.4%) were not statistically different from the values of FEV_1 at the beginning of the continuous infusions (42.7, 19.1%). According to their results, they reported a larger mean change of FEV_1 values after the continuous infusion treatment (9.6, 10.6%) course compared to the short infusion treatment course (5.6, 10.1%). With regards to patients harbouring isolates of *P. aeruginosa*, their results showed that for patients harbouring resistant isolates of the microorganism, the continuous infusion treatment course resulted in a greater change of mean % of predicted FEV_1 (1.7 for the short infusion treatment and 6.2 for the continuous infusion treatment). Furthermore, the mean difference (measured as standard deviation) in the time interval between two successive IV antibiotic treatment courses was greater after the continuous infusion treatment compared to short infusion treatment (3.1 for the continuous infusion treatment and 2.7 for the short infusion treatment). This study also reported a significant mean decrease in C-reactive protein (19.7 mg/litre for the short infusion treatment course and 18.7 mg/litre for the continuous infusion treatment course), leukocyte count (1829 no. of cells/mm^3 for the short infusion treatment course and 2068 no. of cells/mm^3 for the continuous infusion treatment course) and neutrophil count (2047 no. of cells/mm^3 for the short infusion treatment course and 2294 no. of cells/mm^3 for the continuous infusion treatment course).

4.2.6. Adverse events reported

4.2.6.1. Adverse events concerning elastomeric devices

Only one study provided data specific to adverse events caused by elastomeric devices, where only one child out of 34 patients (3%) experienced an elastomeric device failure. However, according to the authors, this was thought to be due to the tip placement of the central line, which directly impacted the emptying of the elastomeric device. This patient's device was changed to a syringe driver and subsequently managed on intermittent bolus doses.

4.2.6.2. Adverse events concerning central venous catheters

Only one study provided data on the type of central venous catheters used and its distributions in their cohort, with 27 patients (79%) used peripherally inserted central catheters (PICC), four patients (12%) used tunnelled central lines, three patients (9%) used a "port-a-cath" in situ. None of the patients that used a "port-a-cath" or tunnelled central lines experienced any mechanical complications, which contrasts with the four patients (15%) that experienced mechanical line complications, using a PICC, where the reasons for this were: occlusion (n=2, 8%) and accidental dislodgement (n=2, 8%). Fortunately, none of the patients within this cohort developed a line infection. In another study, two patients (28.6%) experienced complications from their treatment,

which prompted the removal of their silastic catheters. In these instances, one patient had his catheter removed due to "technical problems" and the other had their silastic catheter occluded.

4.2.6.3. Adverse drug reactions

Two studies reported adverse drug reactions within their cohorts. In one study, authors reported adverse drug reactions (ADRs) in two patients within their cohort, where one child developed Stevens-Johnson syndrome on day 11 of their treatment and the other developed a drug-induced fever. Both ADRs occurred during their course of Piperacillin-Tazobactam. Another study reported a total of 124 adverse events (68 during the short infusion treatment course and 56 during the continuous infusion treatment course) across 50 patients of their cohort. Only 2 out of the 124 adverse events (1.6%) were considered as serious adverse events (one after the short infusion treatment course and one after the continuous infusion treatment course) which led to requiring hospitalisation for pulmonary exacerbation. According to the authors of this study, the most common adverse effects were nausea, abdominal pain, diarrhoea (12%), haemoptysis (11.3%), headaches (7.3%), tonsilitis (6.5%) and pulmonary exacerbations (6.5%). This study also reported a significant increase of aspartate aminotransferase ([AST], 14.2% for short infusion course and 17.8% for continuous infusion course) and alanine aminotransferase levels ([ALT], 19.8% for short infusion treatment course and 24.1% for the continuous infusion treatment course) at the end of each antibiotic course for both regimens. However, with regards to alkaline phosphatase (ALP) and gamma-glutamyl transferase levels (GGT), the authors of the study deemed the changes to be insignificant between the beginning and the end of the treatment courses, regardless of the regimen.

4.2.7. Pharmacokinetics

Only one study included pharmacokinetic data on ceftazidime for 28 patients within their cohort. The mean ceftazidime C_{ss} during the continuous infusion treatment course was 56.2 ± 23.2 µg/ml (values ranged from 37.0 to 65.9 µg/ml, whereas during the ceftazidime short infusion treatment course, the mean C_{max} was 216.3 ± 71.5 µg/ml (values ranged from 172.0 to 247.0 µg/ml), the mean C_4 was 40.7 ± 21.5 µg/ml (values ranged from 24.8 to 56.6 µg/ml), and the mean C_{trough} was 12.1 ± 8.7 µg/ml (values ranged from 6.1 to 16.6 µg/ml). Thus, when comparing the difference in pharmacokinetics between two regimens of treatment, the study showed that the mean C_{ss} was significantly larger than the mean C_{trough} and the mean C_4 (with a P value less than 0.05).

4.3. Discussion

This is the first systematic review of the use of elastomeric devices for antibiotic delivery for children and young people. Given how widespread p-OPAT services are, it is a surprise how there is such a lack of extractable data regarding this topic, however, this provides rationale to perform this

systematic review and an opportunity for us to add to this topic. With data for less than 100 patients, we acknowledge that our sample size is relatively small and attempt to not make sweeping generalisations.

Only seven IV antibiotics have been assessed for delivery through elastomeric devices in children, the most common of these being ceftazidime, which is related to infective exacerbations of cystic fibrosis. In overall clinical practice, the most prescribed IV antibiotic classes by hospital trusts are (by a large margin) penicillins, followed by tetracyclines and macrolides, respectfully (171). Interestingly, 3rd generation cephalosporins, such as ceftazidime, account for a somewhat small proportion of IV antibiotics prescribed by trusts, even though its use has increased by more than 30% from 2015 to 2019 (171). The most common reason to prescribe IV antibiotics rather than oral antibiotics, at least initially, is to treat severe life-threatening infections when there are concerns about not achieving sufficient antibiotic concentrations at the site of infection (172). Other common reasons include patients who are unable to absorb or take oral drugs and for immunocompromised patients due to their inability to fight infections (172), for instance, the use of IV piperacillin/tazobactam for febrile neutropaenia amongst a paediatric oncology population. Piperacillin/tazobactam has many indications due to its broad spectrum of antibacterial activity, which encompasses most gram-positive and gram-negative aerobic and anaerobic bacteria but excels as a treatment for febrile neutropaenia due to the complication being a time-sensitive complication, where the treatment must be provided before blood cultures are identified (173). Although the antibiotics identified within this review do not match the most common IV antibiotics prescribed by trusts, there is rationale for the use of some of the antibiotics identified. Ceftazidime, piperacillin-tazobactam and flucloxacillin exhibit a time-dependant bactericidal effect, where in essence, these antibiotics have a larger efficacy the longer their serum concentrations are higher than the minimum inhibitory concentration (MIC), whilst gentamicin, tobramycin, amikacin and ciprofloxacin display a concentration-dependant bactericidal effect, where these drugs perform more efficaciously when their concentrations are $\geq$ 10 times above the MIC for their target organism (174, 175). Since elastomeric devices utilise the mechanism of continuous infusion, antibiotics that exhibit time-dependant bactericidal effects can be deemed as safer (lower potential of incurring adverse events) and more efficacious than antibiotics that display concentration-dependant bactericidal effects, when considering delivery through elastomeric devices. Moreover, the frequency of intermittent infusions of ceftazidime, flucloxacillin and piperacillin-tazobactam discourage the use of these drugs for p-OPAT, unless administered through a 24-hour continuous infusion through elastomeric devices, where the stability of these drugs further encourages the use of elastomeric devices to deliver these antibiotics (176).

As stated previously, the most common infection across the 90 patients included within this review is exacerbation of cystic fibrosis, where this correlates with the most common microorganism identified, *Pseudomonas aeruginosa*. Although most of all positive microbiological cultures identified *Pseudomonas aeruginosa*, a large proportion of cultures identified *Staphylococcus aureus*, which is supported by the fact that the two of the most common bacteria identified in the mucus of cystic fibrosis patients are *Pseudomonas aeruginosa* and *Staphylococcus aureus* (177, 178). Furthermore, recent research has shown that late-infecting *Pseudomonas aeruginosa* strains develop coexisting interactions with *Staphylococcus aureus*, when previously, it has been a well-known fact that early-infecting *Pseudomonas aeruginosa* strains produce anti-staphylococcal compounds and inhibit the growth of *Staphylococcus aureus* (177). However, the impact of the co-infection between *Staphylococcus aureus* and *Pseudomonas aeruginosa* on the manifestation of cystic fibrosis is debatable (179-181). In terms of the efficacy of treatment within the three included studies, one study reported that their continuous infusion treatment course was more efficacious (larger mean increase of FEV_1 values, larger mean difference in the time interval between two successive IV antibiotic treatment courses, and a larger decrease of leukocyte and neutrophil count) than their short infusion treatment course, with only C-reactive protein levels being reduced more with the short infusion treatment course. The increased efficacy of continuous infusion compared to short infusions of ceftazidime may be due intermittent administrations of ceftazidime, leading to low sub-MIC C_{trough}s and high C_{max}s, whereas a continuous infusion of ceftazidime would lead to a lower C_{max} but the serum concentration of ceftazidime should be higher than the MIC, thus in theory, the percentage of time spent where serum concentrations of ceftazidime are above the MIC is larger in continuous infusions, when compared to intermittent infusions of ceftazidime (169, 182, 183).

In terms of adverse events, studies mainly reported data concerning adverse drug reactions and adverse events relating to central venous catheter, with only one patient experiencing elastomeric device failure. This suggests that the administration of antibiotics through elastomeric devices for a paediatric population can be considered as safe. With regards to problems encountered with central venous catheters, a study noted that only PICC lines caused complications, where the authors theorised that the reason why the elastomeric device failed for that one patient was due to a tip dislodgement of the central line, rather than a problem with the actual device itself. Another study reported that a patient experienced occlusion of their silastic catheter and another patient had "technical issues" with their catheter. Findings from included studies in this review are supported by an observational study evaluating the efficacy and safety of continuous infusions with elastomeric devices for OPAT, where out of 150 patients enrolled, only 16 patients (11%) experienced an adverse event, where most of the adverse events were explained as expected side-effects of the

administered drug (184). This further reinforces that these adverse events do not directly reflect on the elastomeric device, but rather the technicalities of a central venous catheter or the side-effects of a drug itself. In terms of adverse drug events, out of the 90 patients, only piperacillin-tazobactam was identified as a cause for adverse drug events. However, one study identified 124 adverse events within their short and continuous infusion treatment groups (using ceftazidime and tobramycin), where two adverse events were serious adverse events. The same study also reported an increase in ALT and AST within both short and continuous infusion groups, where this data is supported by the fact that ceftazidime can cause LFT (liver function tests) derangement with prolonged courses (185).

Considering how prevalent p-OPAT services are, it comes to a surprise how there was only one study that conducted pharmacokinetic analyses. This study reported the mean C_{ss} of ceftazidime (continuous infusion) to be higher than the mean C_{max} and C_4 of ceftazidime (short infusion), where the C_{ss} remained permanently above the MIC during the continuous infusion. Furthermore, the mean steady-state blood ceftazidime concentration was consistent with the value found in another study that obtained pharmacokinetic data of ceftazidime delivered through continuous infusions to a paediatric population (186). The results from the study that conducted pharmacokinetic analysis show that ceftazidime exhibits time-dependant bactericidal activity and ceftazidime's increased effectiveness when delivered through continuous infusions, which subsequently shows that ceftazidime delivered through elastomeric devices has a larger efficacy than delivered through intermittent delivery methods. Although the other two studies included within this review do not include pharmacokinetic analysis, there are many pre-clinical studies published that include pharmacokinetic analysis of antibiotics that are delivered through elastomeric devices. This lack of clinical pharmacokinetic data will hopefully prompt others to perform pharmacokinetic analysis within their future studies concerning antibiotics delivered through elastomeric devices, in the pursuit of improving the safety and efficacy of these devices.

Quality of life data contained within the results suggest that there a multiple benefits of using elastomeric devices as a delivery mechanism for p-OPAT, such as: the ability for families to get back to their "normal" lives at a quicker rate, children being able to return to school whilst being treated with an elastomeric device and an opportunity for families to be directly involved with their child's treatment, where some families found the option of administering their child's medication through an elastomeric device, a highly favourable one. Moreover, when family members administer their child's treatment, this incurs cost savings (by cutting out the need for a professional to administer) and allows patients to be managed outside of an inpatient setting, especially if there is a limited access to a community nursing team.

With data reflecting only 90 patients gathered amongst 3 studies, we hypothesise reasons and factors for this lack of data (especially when concerning an oncological use for these devices), which include: the role of elastomeric devices in different paediatric cohorts, the popularity of chemotherapy vs. antibiotics delivered through elastomeric devices within a paediatric oncology population and the rationale for the route of antibiotics delivered to paediatric patients. More than 70% of the patients included within this review were being treated for an infective exacerbation of cystic fibrosis, which is warranted as the pharmacokinetics of continuous infusion antibiotic therapy favours the maintenance of antibiotic serum concentrations above the MIC compared to intermittent infusions (187). When concerning the use of elastomeric devices to deliver antibiotics to a paediatric oncology population (e.g., to treat febrile neutropaenia), paediatric patients are more likely to be treated in the hospital as their conditions can deteriorate at a more rapid rate than adults, thus negating the benefits of outpatient antibiotic delivery facilitated by elastomeric devices and ultimately discouraging antibiotic delivery through elastomeric devices amongst this specific cohort. Although outpatient treatment may be recommended to paediatric patients with low-risk febrile neutropaenia, outpatient oral antibiotic therapy is the current recommendation advised by the CCLG, SIOP-endorsed international febrile neutropaenia guideline and many treatment centres around the UK, where this guidance assumes that the patient does not have significant gastrointestinal issues (diarrhoea, vomiting and mucositis) (188, 189). Amongst a paediatric oncology population, a more common use of elastomeric devices is to deliver chemotherapy as a means of ambulatory/home chemotherapy, where this mode of chemotherapy delivery has risen in popularity in countries like Canada and the UK (190-192). The factors stated above contribute largely to the identification of largely CF paediatric population (where p-OPAT is favoured) within our cohort and why we did not identify any paediatric oncology patients (where p-OPAT is generally not favoured).

4.3.1. Limitations and recommendations for future studies

However, some limitations of this systematic review must be noted. Although there seems to be an adequate amount of data on OPAT and p-OPAT, there is a clear lack of clinical data revolving around the antibiotic delivery through elastomeric devices within a paediatric population. Where elastomeric devices have been focused, an adult population seems to be favoured over a paediatric population, which has resulted in a small selection of studies for the evaluation of antibiotic delivery through elastomeric devices amongst a paediatric population. Some data contained within included studies (median age of patients, male/female ratio of patients and median duration of treatment) were not identified and were subsequently not obtained, even after contacting corresponding authors. Furthermore, studies included within this review may not have included data that resonates with the data categories regarding our secondary outcomes, where pharmacokinetic data is an

example of a data category only fulfilled by one study included and the lack of pharmacokinetic data regarding antibiotics identified undermines the evaluation of antibiotics delivered through an elastomeric device for a paediatric population. However, these limitations highlight areas of this topic to be further researched into, improving the evaluation of antibiotics delivered through elastomeric devices and thus, optimising patient care.

4.4. Conclusion

Seven antibiotics have been evaluated for use through an elastomeric device amongst a paediatric population. Limited number of studies have been undertaken surrounding the topic of elastomeric devices within paediatrics, where a relatively large range of antibiotics have been reviewed and no signals have emerged to date, although it is surprising how little information has been published. Antibiotic delivery through elastomeric devices can provide benefits to patient-parent wellbeing, increase cost-effectiveness, and reduce pressure on a healthcare environment, limited research has been undertaken, where data is primarily revolving around cystic fibrosis patients. Other specialist populations (e.g., oncology) may benefit from further research to understand the use of antibiotics through elastomeric devices within particular patient groups.

5. PINGU study

5.1. Introduction

Although survival rates for children with cancer have steadily improved, treatment for childhood cancer remains associated with a substantial risk of short, medium, and long-term adverse effects. Numerous chemotherapeutic drugs are associated with nephrotoxicity, where these drugs can cause significant acute renal damage (glomerular and tubular) in the short term and can result in long-term renal problems. Tubular injury caused by chemotherapy frequently results in magnesium, potassium, and phosphate deficiency, necessitating prolonged electrolyte supplementation and, on rare occasions, can lead to complications such as hypophosphatemic rickets.

Due to the significance of chemotherapy-induced nephrotoxicity, there is a clear need for new markers of nephrotoxicity for patients receiving nephrotoxic chemotherapy, so that patients with renal damage can be identified and monitored as early as possible and so that further damage can be limited, where an example of this would be the restriction and avoidance of concomitant nephrotoxic drugs such as aminoglycoside antibiotics. Neutrophil Gelatinase Associated Lipocalin (NGAL) is a biomarker that appears to identify renal damage, when investigating children receiving nephrotoxic chemotherapy. NGAL is responsible for the growth and differentiation of renal tubular cells and exerts bacteriostatic effects within the distal urogenital tract by altering the bacterial siderophore-mediated iron acquisition (193), where this siderophore-iron-complex NGAL limits proximal tubular damage and diminishes apoptosis. In terms of the quantity of NGAL expression, NGAL is usually expressed at very low levels in several human tissues, including lungs, stomach, kidneys, and the colon (194). However, when damaged (by ischaemia-reperfusion injury, nephrotoxins sepsis or chronic progressive changes), kidney epithelia excrete and express large quantities of NGAL into the urine (195). NGAL has been identified as the protein with the earliest rise and peak after renal ischaemia (195, 196), where NGAL appears to be an early biomarker in contrast to the currently available laboratory markers of renal damage used in everyday clinical practice. Amongst other kidney insults such as: after cardiopulmonary bypass (197), sepsis in critical illness (193), delayed graft function in renal transplantation (198), contrast-induced nephropathy (199), lupus nephritis flares (200) and haemolytic-uraemic syndrome (201), urinary NGAL has been identified as a potential early marker of renal injury in children.

Unfortunately, to this date, information revolving around NGAL as a biomarker for early detection of renal damage in children receiving nephrotoxic chemotherapy is quite limited. There appears to be only 1 previous publication of the use of the NGAL biomarker in patients receiving chemotherapy, where this study compromised of 12 adult patients. Within this study, urinary NGAL levels increased significantly more in patients receiving cisplatin, who subsequently developed AKI, compared to

controls at up to 15 days after cisplatin administration, where there was also a marked NGAL increase at day 2 after cisplatin administration, which predicted acute kidney injury (>25% serum creatinine increase vs. baseline) (202).

An apparent challenge to this cause and paediatric oncology alike would be the nephrotoxicity associated with antibiotics, where many centres (including Alder Hey) prescribe aminoglycosides as first line antibiotics for treatment of febrile neutropaenia (FN) episodes, where as many as 10-25% of therapeutic courses of aminoglycosides are complicated by nephrotoxicity, despite close patient monitoring (203). This emphasises the clear need for an early marker of kidney injury amongst children receiving nephrotoxic chemotherapy, to prevent further damage that could be caused by aminoglycosides (by switching them to non-nephrotoxic antibiotics). Furthermore, NGAL levels have also been detected to be elevated in various types of adult-type cancers including adenocarcinomas of the breast, bowel and urothelial carcinomas (204, 205). However, according to existing reports, elevated urinary NGAL levels have only been detected in brain tumours (medulloblastoma) amongst a paediatric population (206).

5.1.1. Objectives

This study is a part of "The PINGU Project" – The Prospective Investigation Into NGAL Utility, which has been conducted at the Alder Hey Children's NHS Foundation Trust in Liverpool, UK.

The objectives of the PINGU study are to: determine the utility of NGAL in predicting AKI amongst a paediatric oncology patient group that are at risk of renal damage, correlate urinary and blood measurements of NGAL in a group of patients within the study cohort, and finally, to prompt further studies that investigate the effect of early intervention would have on improving the renal outcome for these patients.

With regards to the progress of the study, all aspects of data collection (serum and biochemistry data) from samples of consented patients were performed by a team of researchers that have no affiliation with the project currently. This data was stored in various areas, which include excel sheets, patient case report files and other patient records, where all the data were either in a secured Alder Hey cloud drive or were paper documents that were in secured locations within the hospital. My role within this study was to perform data cleaning (obtain and compile demographic, urinary and biochemistry data from mentioned sources) and perform data analysis to investigate the relationship between urinary NGAL and cisplatin-induced nephrotoxicity.

5.2. Methods

As it is known that plasma and urinary levels of NGAL can be elevated amongst some pathologies (sepsis, brain tumours, Down's syndrome) and some patients enrolled may be afflicted by some of

these conditions, the study has aimed to measure baseline NGAL levels prior to the start of nephrotoxic therapy, where it will then be compared to with subsequent levels of NGAL of when patients are exposed to nephrotoxic chemotherapeutic agents. Although I was not directly involved in this process, the PINGU study has obtained ethical approval prior to the data collection process, where the study protocol is contained within ***Appendix 1***. In terms of the assessment of AKI, the study has used the RIFLE criteria to assess AKI, where ***Table 3*** includes exact definitions for each stage.

Table 3. RIFLE criteria

Stage	Criteria
Stage I (Risk)	Increased creatinine (x1.5) or decreased GFR > 25% or urine output < 0.5ml/kg/h x 6 hours
Stage II (Injury)	Increased creatinine (x2) or decreased GFR > 50% or urine output < 0.5ml/kg/h x 12 hours
Stage III (Failure)	Increased creatinine (x3) or decreased GFR > 75% or urine output < 0.5ml/kg/h x 24 hours or anuria x 12 hours

5.2.1. Patient selection criteria

The study will include 2 groups of patients: patients receiving nephrotoxic chemotherapy and patients receiving nephrotoxic chemotherapy along with receiving aminoglycosides. In terms of the eligibility of the former group, patients must receive one or more of the following nephrotoxic drugs: cisplatin, ifosfamide and high dose methotrexate, and must provide informed written consent. In terms of the eligibility of the latter group, patients must be receiving either cisplatin, ifosfamide or high-dose methotrexate (or a combination of them) up to 4 weeks prior to their admission and receiving aminoglycosides on their current admission, where they must also provide informed written consent. The exclusion criteria for both groups are the same, where patients with urinary tract infections will be excluded from the study.

In terms of the write-up for the thesis, we will only be focusing on the patient group that had cisplatin administered.

5.2.2. Diagnostic investigations during the study

5.2.2.1. Patients receiving nephrotoxic chemotherapy

Urinary NGAL (uNGAL) has been taken: prior to chemotherapy, daily until the end of administration of nephrotoxic chemotherapy, on days 7 and 10 (for patients receiving cisplatin and ifosfamide only), at their first clinic appointment after the end of their treatment, and 6 and 12 months after the end of their treatment. Considering “Day 1” as the day of admission for each course of chemotherapy, “Day 7” and “Day 10” urinary NGAL samples will be obtained at home following discharge from the hospital. Patients will be provided by informative leaflets, which depict the taking and handling on samples, providing patients with clear instructions for the timing of these samples. With regards to urine samples taken at home, clean catch samples will be required to minimise contamination of samples, and when concerning younger patients (particularly infants and toddlers), parents will be instructed how to provide these samples. For each urine sample, appropriate sample tubes, instructions and pre-addressed and stamped packaging are provided. This has allowed for samples to be taken at home and sent via recorded delivery to a predesignated individual within the Paediatric Oncology Research Department at Alder Hey, where from here, they have been taken to the receiving laboratory for processing and storage. If deemed necessary, urine samples are stored in the patient’s fridge at home and are collected within 24 hours by a member of the research team after communication with the family. If the patient is attending hospital with complications of treatment (e.g. FN) or other routine attendance (e.g. supportive treatment/routine bloods/chemotherapy) between “Day 7” and “Day 14”, samples are taken at the predesignated time points where appropriate, where a urine dipstick may also be performed, if additions samples may

be taken. However, just to iterate, no patients has been asked to attend hospital solely for the purposes of providing a urine sample at any point of their treatment.

Serum NGAL (sNGAL) has been taken: prior to chemotherapy, daily until the end of administration of nephrotoxic chemotherapy, at the first clinic appointment after the end of treatment and 12 months after the end of treatment.

"Oncology Profile", which includes urea, creatinine, sodium, potassium, bicarbonate, anion gap, magnesium, calcium and phosphate has been taken: prior to chemotherapy, daily until the end of administration of nephrotoxic chemotherapy, at the first clinic appointment after the end of treatment and 12 months after the end of treatment.

"Urine Biochemistry", which includes urine dipstick (blood, protein, glucose), urine albumin/creatinine ration, retinol binding protein (RBP), phosphate, calcium and creatine has been taken: prior to chemotherapy, daily until the end of administration of nephrotoxic chemotherapy (except for phosphate, calcium and creatinine – where these were only taken on the last day of chemotherapy), at the first clinic appointment after the end of treatment and 6 and 12 months after the end of treatment.

GFR (Cr EDTA excretion) has been taken: before alternate courses of chemotherapy and at the end of chemotherapy.

Urinary NGAL levels that are below the lower limit of detection (<10 ng/mL) will be considered as "0 ng/mL" for analysis concerning mean urinary NGAL values.

Unfortunately, there was data that I could not find (specifically, pre-dose creatinine values for some samples of patients), however, this was not within my control as I was not responsible for any aspect of the data collection process of the PINGU study. Nevertheless, I made attempts to find missing data (contact members that performed data collection for the PINGU study, search through the Alder Hey Meditech database and thoroughly searching through case report files and patient records). When concerning these missing pre-dose creatine values, I have labelled these missing values as "N/A" and subsequently, the affected patients' p-RIFLE stage as "N/A".

5.3. Results

5.3.1. Demographic data

According to data collected, from June 2012 to June 2017, there were 26 patients enrolled in the PINGU study, however only 21 patients were prescribed with at least a single course of cisplatin during their treatment plan (where patients 3, 9, 12, 16 and 21 were not prescribed cisplatin during the study duration and therefore excluded from this analysis). The cohort compromised of 13 males

(61.9%) and 8 females (38.1%), where the mean age of the cohort is 8 years old. Patient demographics, cohort renal function (with p-RIFLE staging) and oncological profile amongst these patients are summarised in ***Table 4***, ***Table 5,*** and ***Table 6***, respectively. When considering criteria for p-RIFLE, only creatinine and GFR will be used to grade p-RIFLE stages, as data revolving urine output was not collected from patients.

Table 4. Cohort demographics

	Study cohort
Number of patients (n)	21
Male (%)	61.9
Mean age of patients (in years)	8
Median age of patients (in years)	7
Age range (in years)	3-17
Proportion of diagnosis (n)	• Osteosarcoma (5) • Medulloblastoma (4) • Hepatoblastoma (3) • Neuroblastoma (3) • Intracranial germ cell tumour (2) • Low grade glioma (1) • Pilocytic astrocytoma (1) • Nasopharyngeal carcinoma (1) • PNET (1)

Table 5. Cohort renal function (with p-RIFLE staging)

Patient ID	Age (years)	Sex (M/F)	Normal range of creatinine (umol/L)	Pre-dose creatinine (umol/L)	% increase/decrease from normal range of creatinine	Normal average GFR for sex/age ($1.73/m^2$)	Pre-dose GFR ($1.73/m^2$)	% increase/decrease from normal average GFR for sex/age	p-RIFLE stage
1	7	F	27 – 57	42	WITHIN NORMAL RANGE	133.0±27.0	159.77	WITHIN NORMAL RANGE (+20.1%)	NORMAL
2	5	F	27 – 57	48	WITHIN NORMAL RANGE	133.0±27.0	150.1	WITHIN NORMAL RANGE (+12.9%)	NORMAL
4	2	F	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
5	8	M	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
6	13	F	27 – 57	N/A	N/A	126.0±22.0	N/A	N/A	N/A
7	6	M	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
8	4	F	27 – 57	45	WITHIN NORMAL RANGE	133.0±27.0	131.54	WITHIN NORMAL RANGE (-1.10%)	NORMAL
10	6	F	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
11	11	M	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
13	17	M	27 – 57	N/A	N/A	140.0±30.0	N/A	N/A	N/A

14	12	M	27 – 57	56	WITHIN NORMAL RANGE	133.0±27.0	91.45	-31.2%	STAGE I (RISK)
15	3	M	27 – 57	23	-17.4%	133.0±27.0	144.67	WITHIN NORMAL RANGE (+8.77%)	NORMAL
17	4	M	27 – 57	N/A	N/A	133.0±27.0	172.5	+29.7	NORMAL
18	9	M	27 – 57	46	WITHIN NORMAL RANGE	133.0±27.0	76.5	-42.5%	STAGE I (RISK)
19	16	M	27 – 57	53	WITHIN NORMAL RANGE	140.0±30.0	115.04	WITHIN NORMAL RANGE (-17.8%)	NORMAL
20	4	F	27 – 57	N/A	N/A	133.0±27.0	N/A	N/A	N/A
22	15	M	27 – 57	N/A	N/A	140.0±30.0	N/A	N/A	N/A
23	9	M	27 – 57	32	WITHIN NORMAL RANGE	133.0±27.0	114.56	WITHIN NORMAL RANGE (-13.9%)	NORMAL
24	4	M	27 – 57	N/A	N/A	133.0±27.0	102.46	-23.0%	NORMAL
25	8	M	27 - 57	58	+1.75%	133.0±27.0	102	-23.3%	NORMAL
26	7	F	27 - 57	46	WITHIN NORMAL RANGE	133.0±27.0	89.2	-32.9%	STAGE I (RISK)

Table 6. Cohort oncological profile

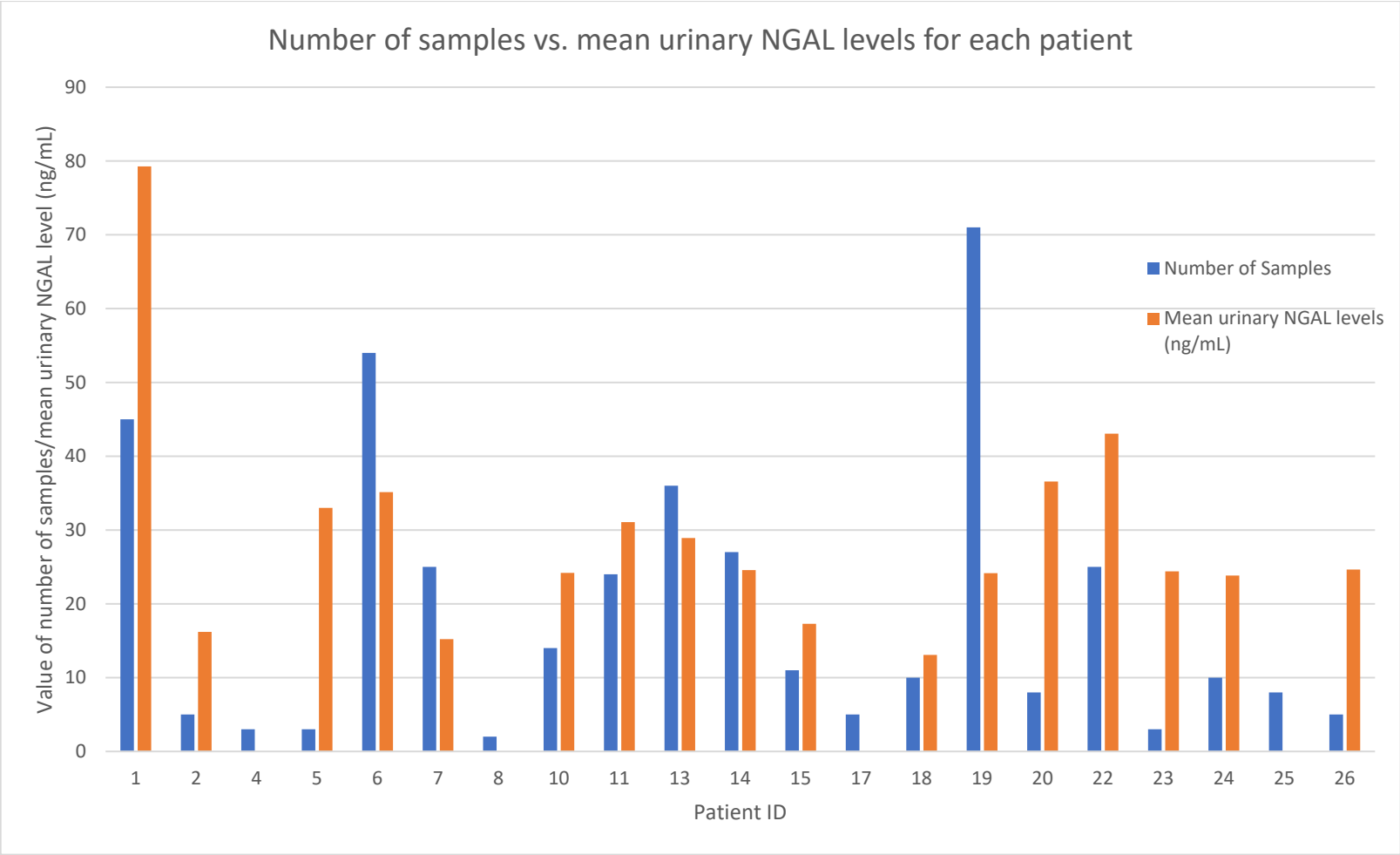
Total number of recorded samples that included all aspects of "oncology profile" across the 21 patients that had at least one dose of cisplatin (n)				146
Aspect of "oncology profile"	Number of abnormal samples (n)	Normal range	Range observed by recorded samples	Mean
Urea (mmol/L)	22	2.3 – 6.4	1.3 – 10.4	3.53
Creatinine (umol/L)	16	27 – 57	19 – 67	47.5
Potassium (mmol/L)	5	3.5 – 5.5	3.2 – 5.1	3.99
Sodium (mmol/L)	27	135 – 145	128 – 167	135
Magnesium (mmol/L)	51	0.78 – 1.02	0.4 – 14.8	0.973
Chloride (mmol/L)	15	100 – 110	94 – 118	105
Bicarbonate (mmol/L)	5	18 – 29	14 - 27	21.6
Albumin (g/L)	51	37 – 53	28 – 44	35.6

5.3.2. Urinary data

5.3.2.1. Mean urinary NGAL levels vs. number of samples (per patient)

A total of 394 samples were collected from the study cohort, where the mean urinary NGAL value from all of the samples is 39.9 ng/mL and the mean number of samples provided per patient was 18.8 samples. The median number of samples provided per patient was 10 samples, where the range of samples provided per patient was from 2 samples to 71 samples. Patient 19 provided the largest number of samples (71) and their mean urinary NGAL value is 24.1 ng/mL, whereas patient 8 was the patient to provide the lowest amount of samples (2), where their mean urinary NGAL value was <10 ng/mL (below lower limit of detection). Patient 1 had the largest mean urinary NGAL level recorded amongst the cohort (79.3 ng/mL), where they provided 45 samples. 4 patients (4, 8, 17, 25) provided 18 samples in total, but all of their samples were regarded as "below the lower limit of detection" due to the lack of precision of the instrument at measuring urinary NGAL levels below 10 ng/mL. Data relating to this section has been displayed within a figure below (***Figure 2***).

Figure 2. Mean urinary NGAL levels vs. number of samples for each patient

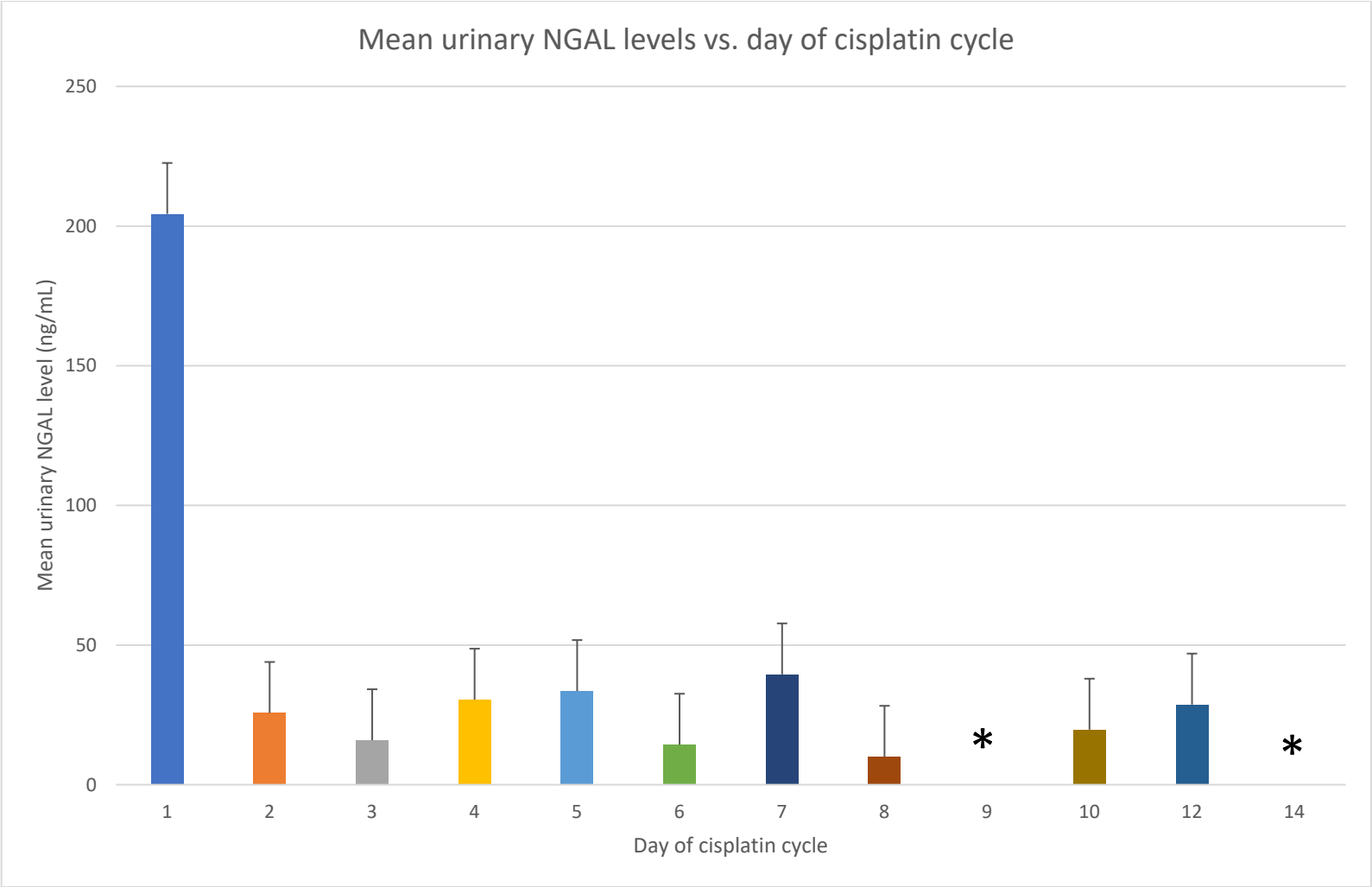


*Lower limit is <10 ng/mL, values <10 ng/mL are marked as zero on this figure.

5.3.2.2. Mean urinary NGAL levels vs. day of cisplatin cycle

Considering that cisplatin cycles can last up to 14 days, the mean urinary NGAL level for this cohort, for each day, is 43.1 ng/mL. For all 14 days, the mean urinary NGAL levels ranged from <10 ng/mL to 204 ng/mL. Day 1 samples compromised of the largest mean urinary NGAL level (204 ng/mL), whereas all samples from day 9 and 14 were "undetectable", providing the lowest mean urinary NGAL levels in the terms of days of cisplatin cycle. Data relating to this section is displayed in the figure below (***Figure 3***).

Figure 3. Mean urinary NGAL levels vs. day of cisplatin cycle



*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

It is evident that the mean urinary NGAL levels on day 1 (baseline) are significantly larger than on other days. ***Table 7*** displays the demographics of 2 groups of patients, one that showed high “day 1” (baseline) urinary NGAL levels and one that showed low “day 1” (baseline) urinary NGAL levels.

Table 7. Demographics of patients that displayed high "day 1" (baseline) urinary NGAL levels vs. demographics of patients that displayed low "day 1" (baseline) urinary NGAL levels

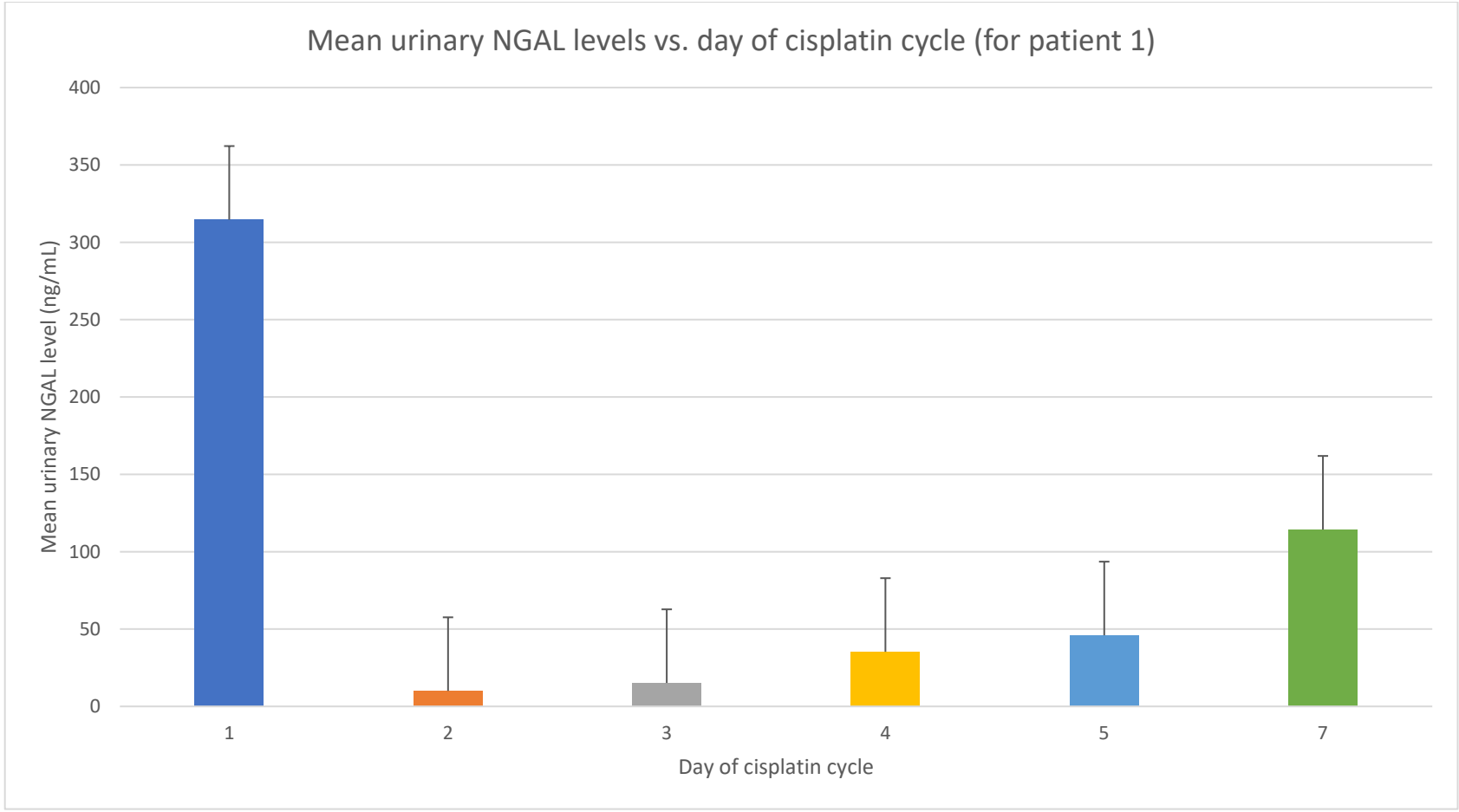
	Patient ID	Age (years)	Sex (M/F)	Mean "day 1" urinary NGAL levels (ng/mL)	Diagnosis	p-RIFLE stage
Group A (high "day 1" urinary NGAL levels)	1	7	F	314.6	Osteosarcoma	NORMAL
	6	13	F	237.1	Osteosarcoma	N/A
	5	8	M	27.3	Medulloblastoma	N/A
Group B (low "day 1" urinary NGAL levels)	13	17	M	17.9	Hepatoblastoma	N/A
	2	5	F	<10	Low grade glioma	NORMAL
	4	2	F	<10	Neuroblastoma	N/A
	7	6	M	<10	Intracranial germ cell tumour	N/A
	8	4	F	<10	Medulloblastoma	NORMAL
	10	6	F	<10	Neuroblastoma	N/A
	11	11	M	<10	Osteosarcoma	N/A
	14	12	M	<10	Germinoma	STAGE I (RISK)

	15	3	M	<10	Hepatoblastoma	NORMAL
	17	4	M	<10	Hepatoblastoma	NORMAL
	18	9	M	<10	Medulloblastoma	STAGE 1 (RISK)
	19	16	M	<10	Osteosarcoma	NORMAL
	20	4	F	<10	Pilocytic astrocytoma	N/A
	22	15	M	<10	Osteosarcoma	N/A
	23	9	M	<10	Nasopharyngeal carcinoma	NORMAL
	24	4	M	<10	Neuroblastoma	NORMAL
	25	8	M	<10	PNET	NORMAL
	26	7	F	<10	Anaplastic medulloblastoma	STAGE I (RISK)

Reviewing data from ***Table 7***, only four out of 21 patients within this cohort have a mean baseline urinary NGAL levels (from their respective samples) higher than the detectable level (<10 ng/mL). Out of these 4 patients, 3 patients belong to "Group A" (high baseline urinary NGAL levels), where the diagnoses of the 2 groups does not seem to show any relevant differences.

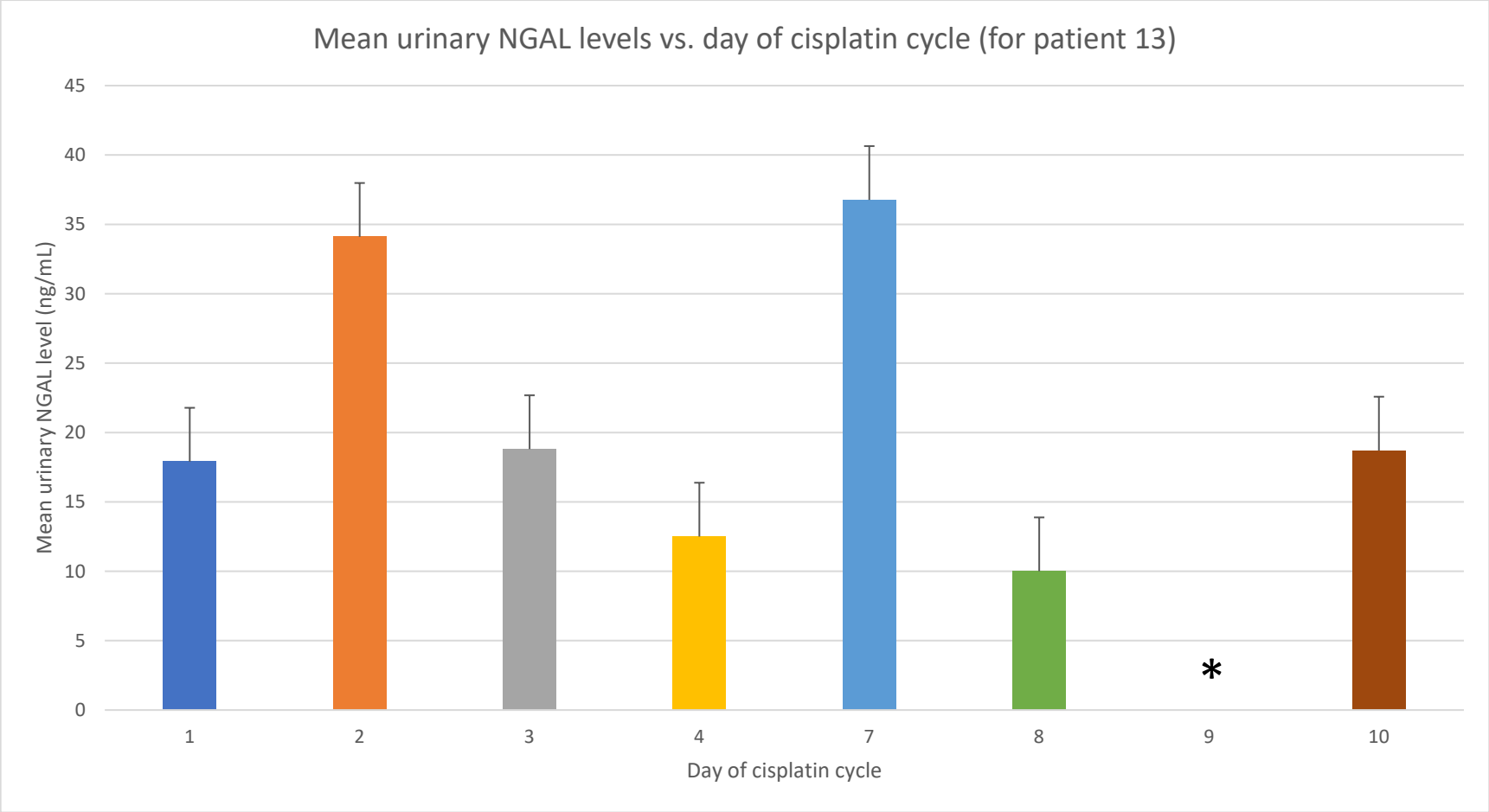
When concerning "Group A", two out of three patients suffered from osteosarcoma and the other patient suffered from a medulloblastoma. Their collective mean baseline urinary NGAL was 193 ng/mL, the group had a 1:2 male-to-female ratio and their median age was 8 years (age range of seven to 13). Two patients within this group did not have their pre-dose creatinine recorded and therefore, none of the patients within this group scored an abnormal p-RIFLE grade. Data regarding the one of the explained patients from "Group A" (patient 1) is displayed within the figure below (***Figure 4***), where other individual patient graphs (patient 6 and 5) are contained within ***Appendix 2***.

Figure 4. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 1)



Interestingly, when concerning “Group B”, this group had three patients (16.7%) that scored abnormal p-RIFLE grades (who had all scored “stage I”). Group B had a total of 18 patients, where only one patient had a mean baseline urinary NGAL level higher than the detectable level of NGAL (<10 ng/mL), where this patient suffered from hepatoblastoma. Within this group, three patients suffered from hepatoblastoma, three patients suffered from osteosarcoma, three patients suffered from neuroblastoma, three patients suffered from medulloblastoma (with one patient suffering from anaplastic medulloblastoma), where other diagnoses included intracranial germ cell tumour, low grade glioma, nasopharyngeal carcinoma, PNET, pilocytic astrocytoma and germinoma (for these diagnoses, n = 1). The group had a 2:1 male-to-female ratio and the median age of the group was 6.5 years old. Considering both facts that patient 13 had the only detectable mean baseline urinary NGAL level and the 3 patients that scored abnormal p-RIFLE grades, data regarding explained patient (patient 13) is displayed within the figure below (***Figure 5***), where other individual patient graphs (patients 14, 18 and 26) are contained in ***Appendix 3***.

Figure 5. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 13)

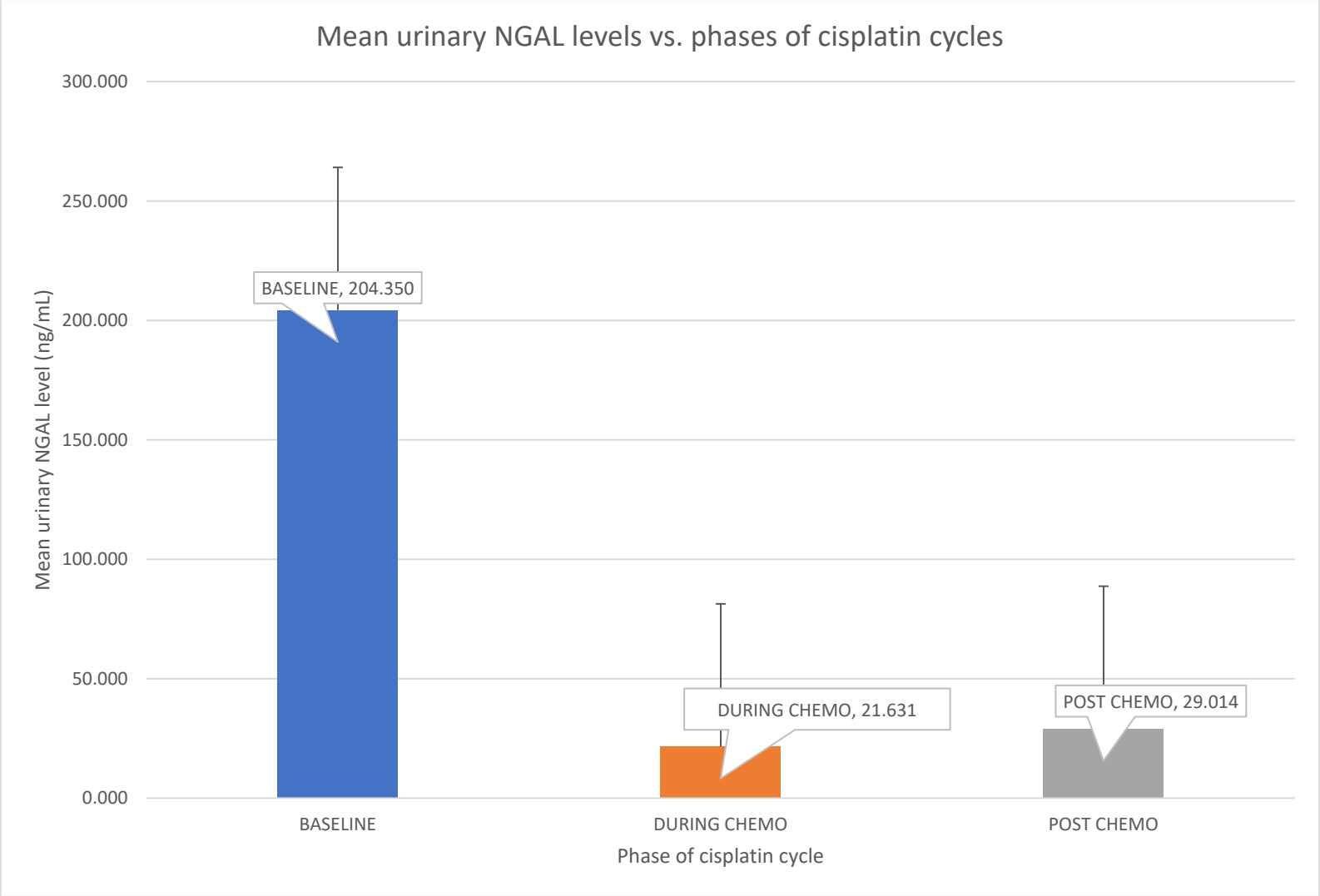


*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

5.3.2.3. Mean urinary NGAL levels vs. phases of cisplatin cycles

Phases of cisplatin cycles are defined as: “baseline” (prior to cisplatin administration), “during chemo” (during cisplatin administration), “post chemo” (shortly after cisplatin administration) and “follow up” (at least 6 months must elapse from finishing their last cisplatin course). Considering that none of the “follow up” samples resulted with detectable levels of urinary NGAL, the “follow up” phase will not be displayed within the figures relating to this section. The “baseline” phase of cisplatin cycles resulted in the largest mean urinary NGAL value within this cohort (204 ng/mL) and the “during chemo” phase resulted in the lowest mean urinary NGAL value within this cohort (21.6 ng/mL), with the “post chemo” phase resulting in a mean urinary NGAL that is slightly larger (29.0 ng/mL). Data relating to this section is displayed in the figure below (***Figure 6***).

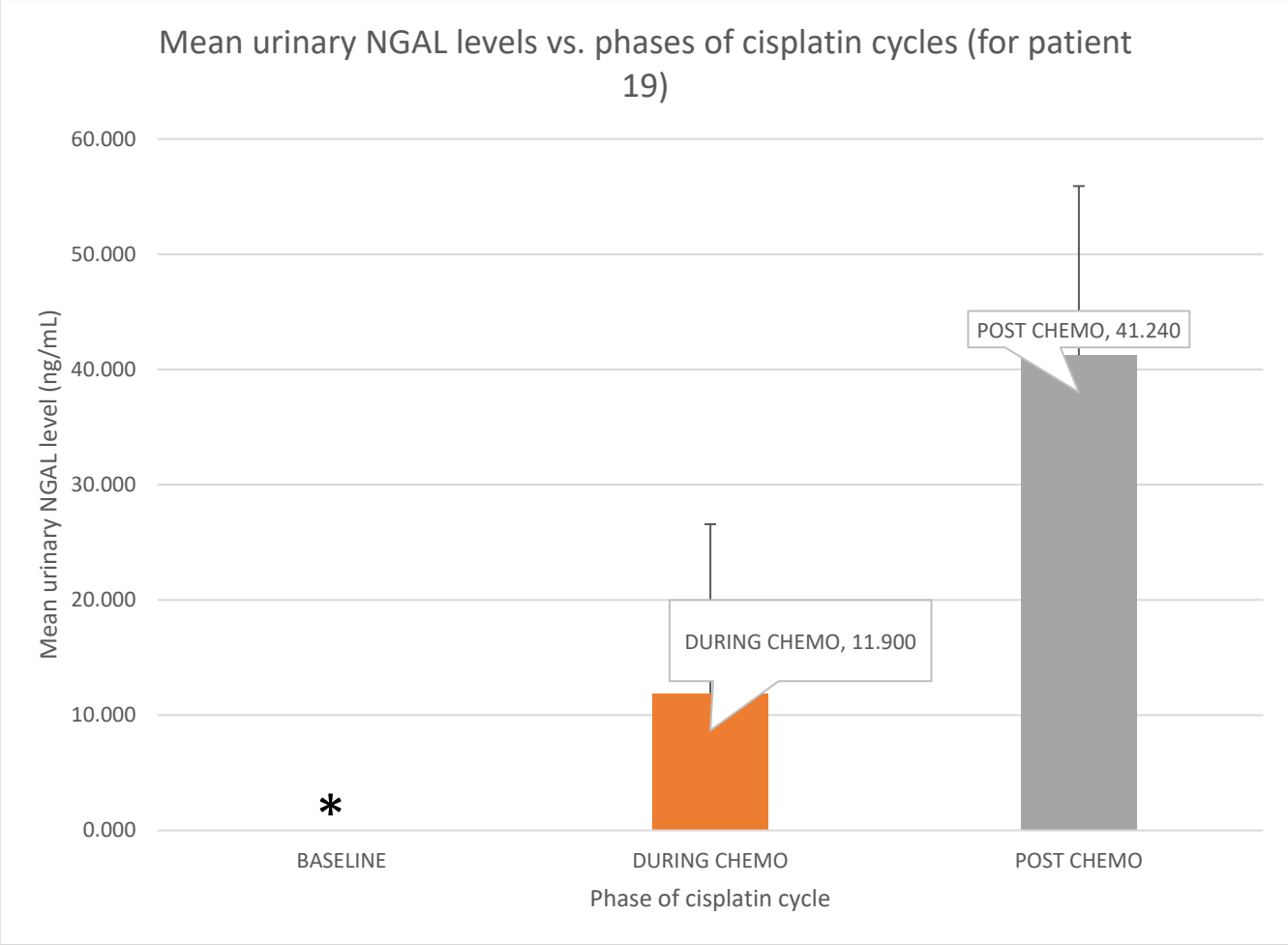
Figure 6. Mean urinary NGAL levels vs. phases of cisplatin cycles



The data contained above in ***Figure 6*** is similar with the data from the previous section (mean urinary NGAL vs. day of cisplatin cycle), where unexpectedly, "baseline" (day 1) values seem to have significantly larger values of urinary NGAL than other days/phases. However, some patients (2, 5, 7, 11, 14, 15, 18, 19, 20, 23, 24) have been observed to display larger mean urinary NGAL values during the "post chemo" phase than any other phase, suggesting that the accumulation of cisplatin exposure may cause a rise in urinary NGAL. However, urinary NGAL values from the rest of the patients suggest that there may not be a correlation between an increase in urinary NGAL values as a cisplatin cycle phases through. Interestingly, patient 13 is the only patient that is observed to show a larger mean urinary NGAL during their "during chemo" phase compared to any other phases.

With regards to the group observed to display larger mean urinary NGAL values during the "post chemo" phase compared to any other phase, 2 patients were treated for medulloblastoma, where other diagnoses included osteosarcoma, germinoma, intracranial germ cell tumour, hepatoblastoma, pilocytic astrocytoma, nasopharyngeal carcinoma, and neuroblastoma (all n = 1). The mean age of this group is 7.9 years old, where the age range for this group is from 3 to 16 years old. Data regarding an explained patient (patient 19) is displayed within the respective figure below (***Figure 7***), where other individual patient graphs (patients 5 and 14) are contained in ***Appendix 4***.

Figure 7. Mean urinary NGAL levels vs. phases of cisplatin cycles (for patient 19)

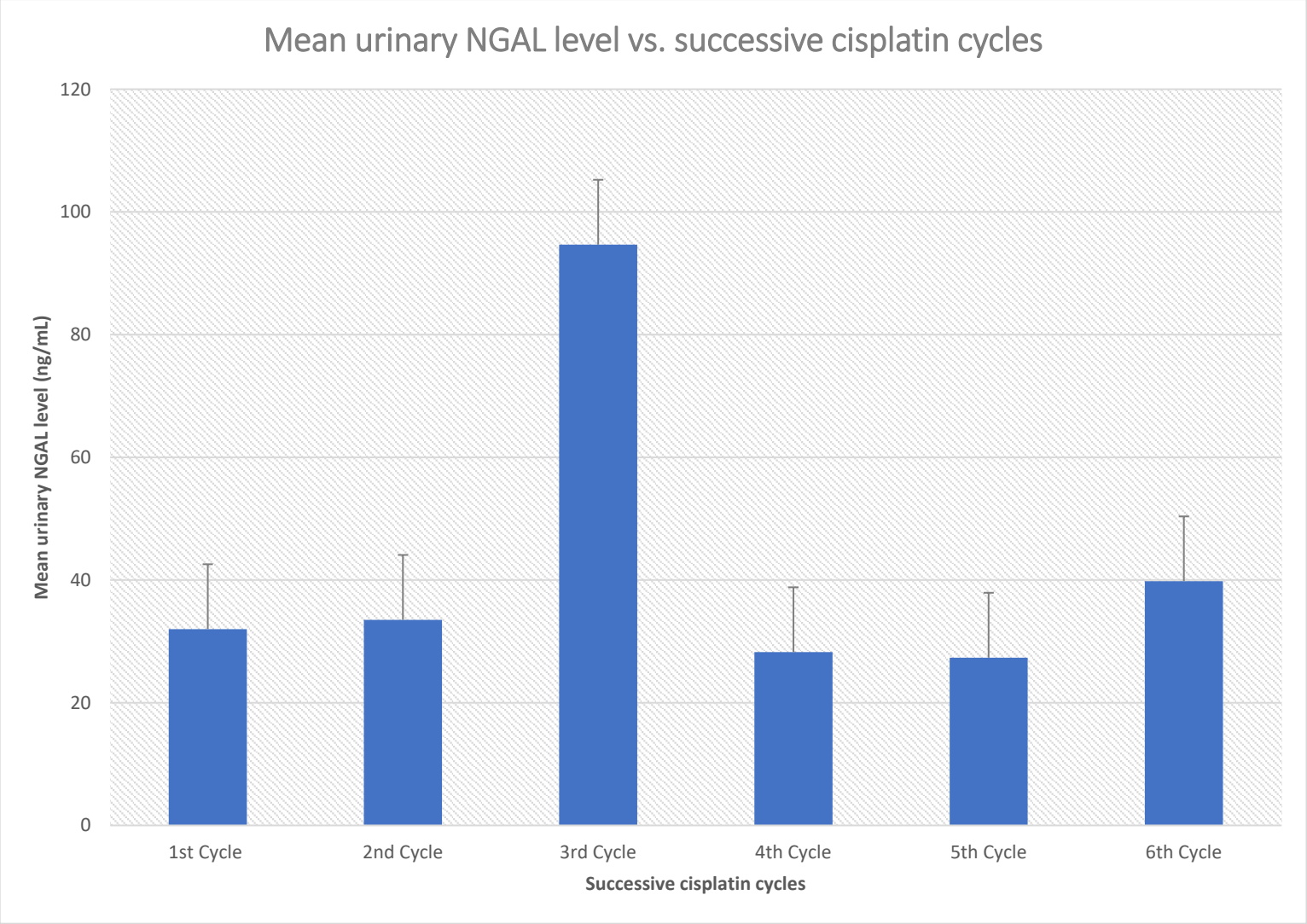


*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

5.3.2.4. Mean urinary NGAL levels vs. successive cisplatin cycles

As many patients within this cohort experienced successive cycles of cisplatin (up to 6 successive cycles), an analysis was performed to observe the relationship between mean urinary NGAL levels vs. successive cisplatin cycles. According to the analysed data, the 3rd successive cisplatin cycle resulted in the highest mean urinary NGAL level (94.7 ng/mL) and the 5th successive cisplatin cycle resulted in the lowest mean urinary NGAL level (27.35 ng/mL). Data relating to this section is displayed in the figure below (***Figure 8***).

Figure 8. Mean urinary NGAL levels vs. successive cisplatin cycles



According to the data above, there does not appear to be a trend other than mean urinary NGAL levels increasing from the 2nd successive cisplatin cycle to the 3rd successive cisplatin cycle, where there is a drastic increase in mean urinary NGAL level from the 2nd successive cisplatin cycle (33.5 ng/mL) to the 3rd successive cisplatin cycle (94.6 ng/mL). Although the data goes against the hypothesis that mean urinary NGAL levels should increase after successive cisplatin cycles, the data above could be explained by anomalous data observed through patient 1, where they were the only patient to display a significantly higher mean urinary NGAL level (compared to other successive cycles) during their 3rd successive cisplatin cycle (199 ng/mL). Data relating to patient 1's mean urinary NGAL levels vs. successive cisplatin cycles and mean urinary NGAL levels vs. successive cisplatin cycles (without data from patient 1) will be presented in respective figures below (***Figure 9*** and ***Figure 10***).

Figure 9. Mean urinary NGAL levels vs. successive cisplatin cycles (for patient 1)

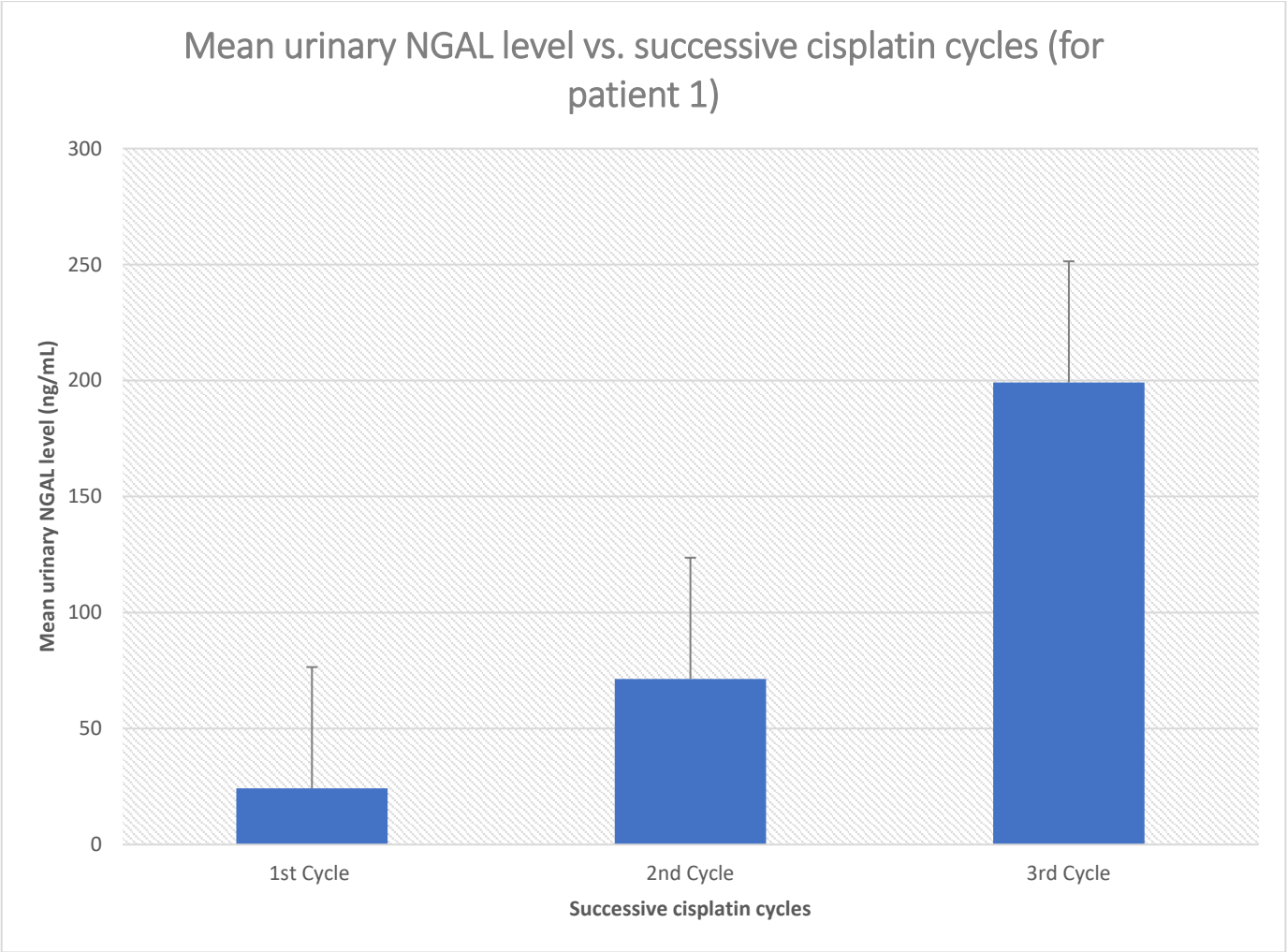
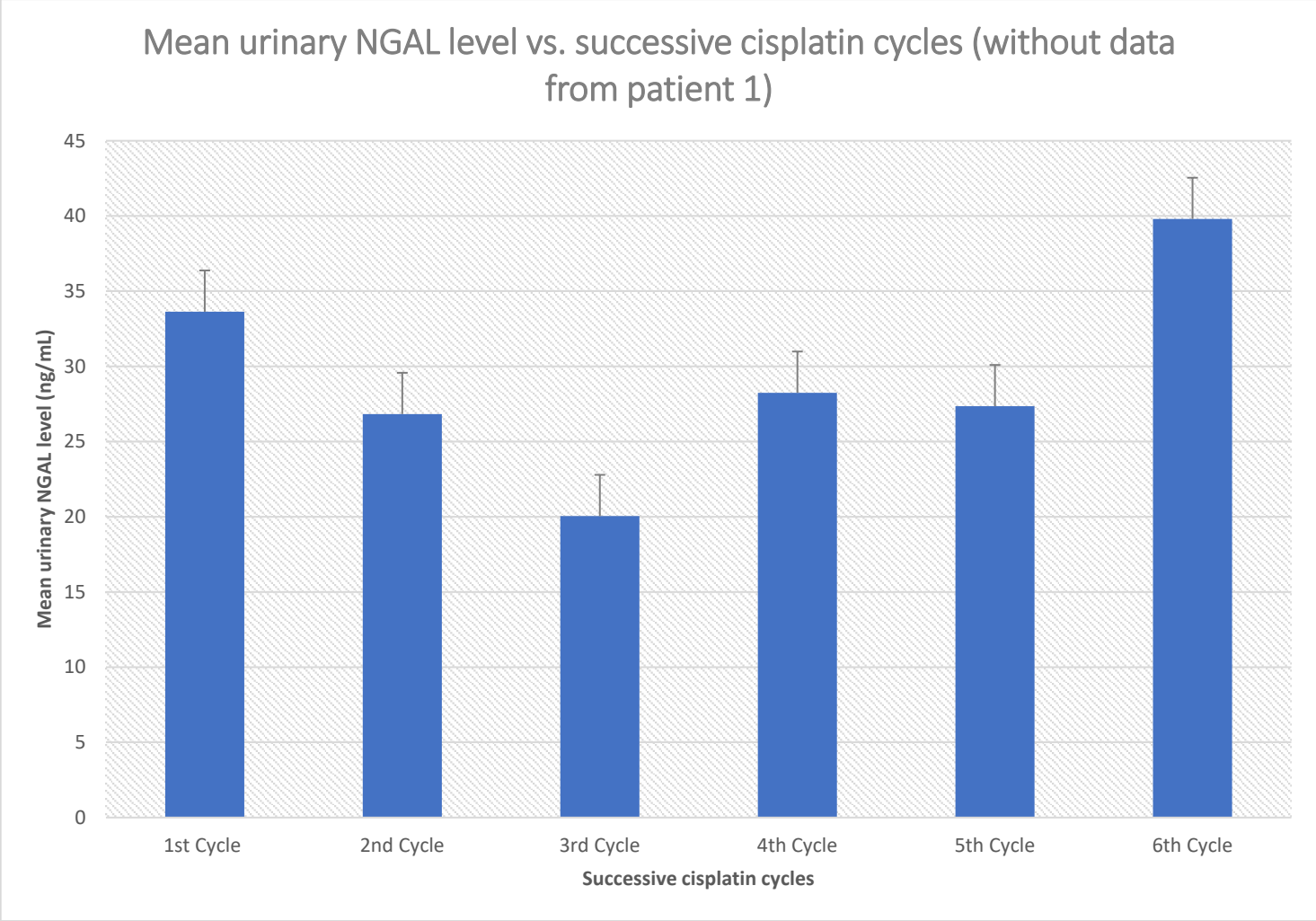


Figure 10. Mean urinary NGAL levels vs. successive cisplatin cycles (without data from patient 1)



With regards to the data above, according to mean urinary NGAL levels vs. successive cisplatin cycles (excluding data from patient 1), the 6th successive cisplatin cycle was observed with the highest mean urinary NGAL level (39.8 ng/mL) and the 3rd successive cisplatin cycle was observed with the lowest mean urinary NGAL level (20.04 ng/mL). However, within the data above, patient 13 was the only patient that underwent the 6th successive cycles of cisplatin and therefore, the only patient to have "detectable" levels of urinary NGAL during their 6th cisplatin cycle. Data relating to patient 13's mean urinary NGAL levels vs. successive cisplatin cycles and mean urinary NGAL levels vs. successive cisplatin cycles (without data from patient 1 and 13) will be presented in respective figures below (***Figure 11*** and ***Figure 12***).

Figure 11. Mean urinary NGAL levels vs. successive cisplatin cycles (for patient 13)

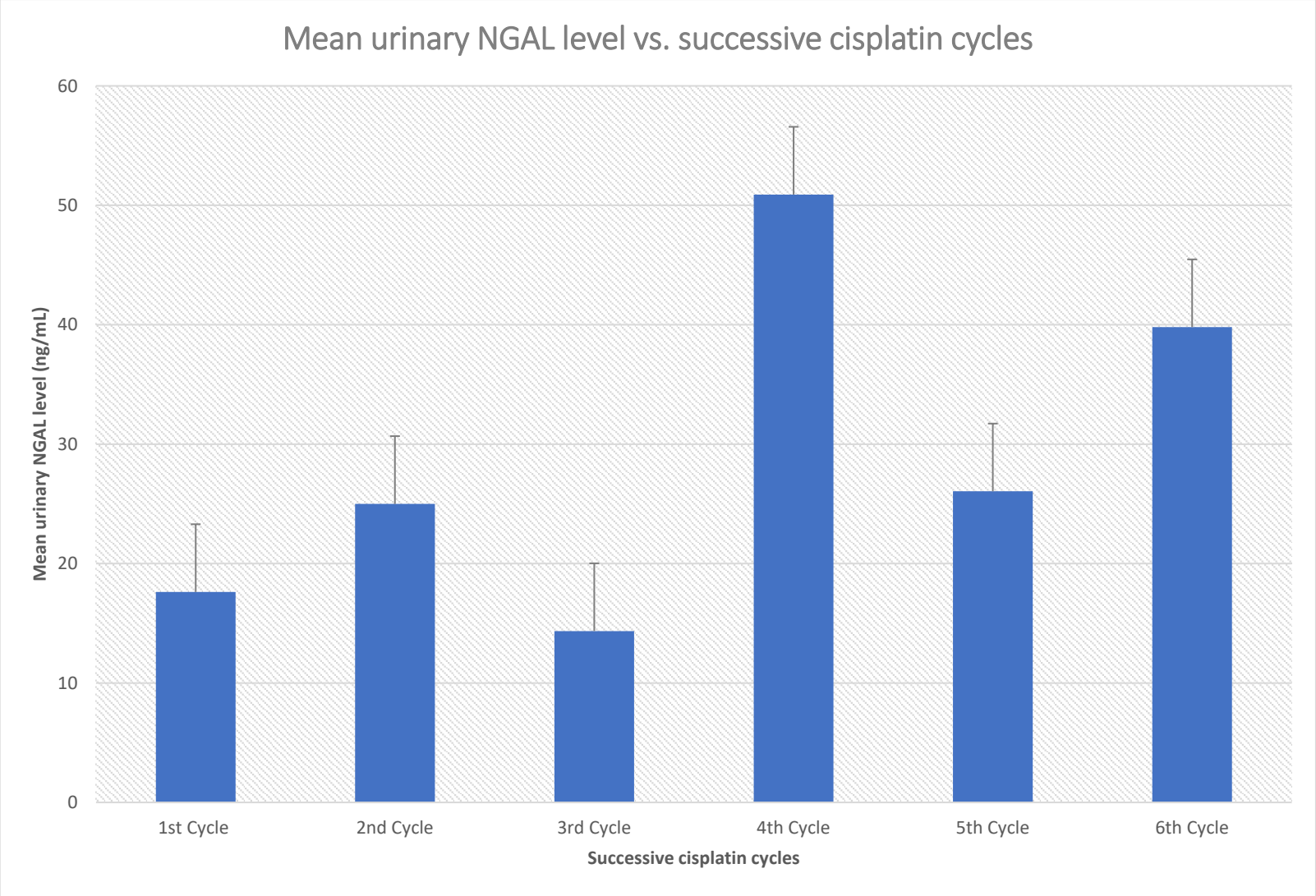
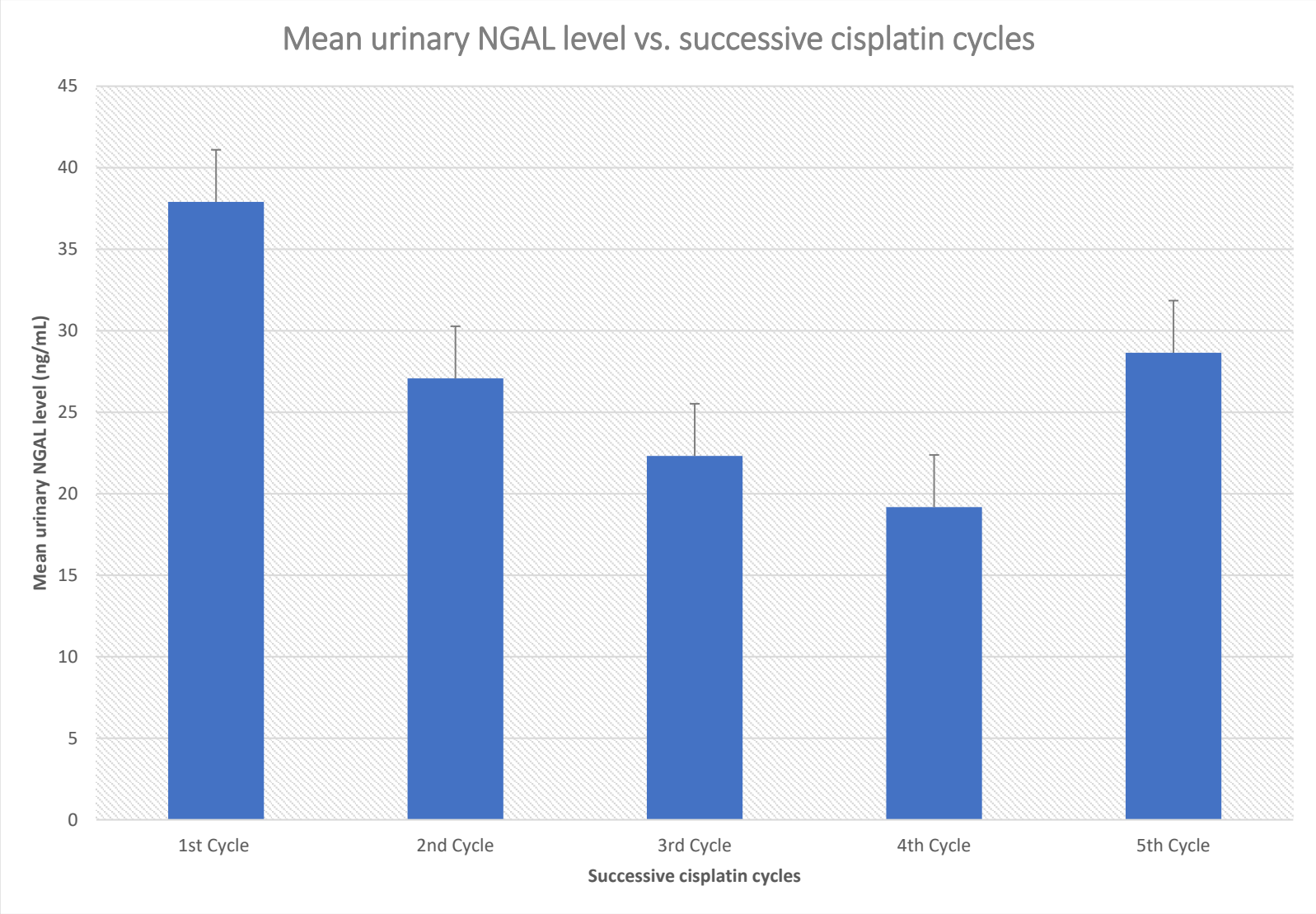


Figure 12. Mean urinary NGAL levels vs. successive cisplatin cycles (without data for patient 1 and 13)

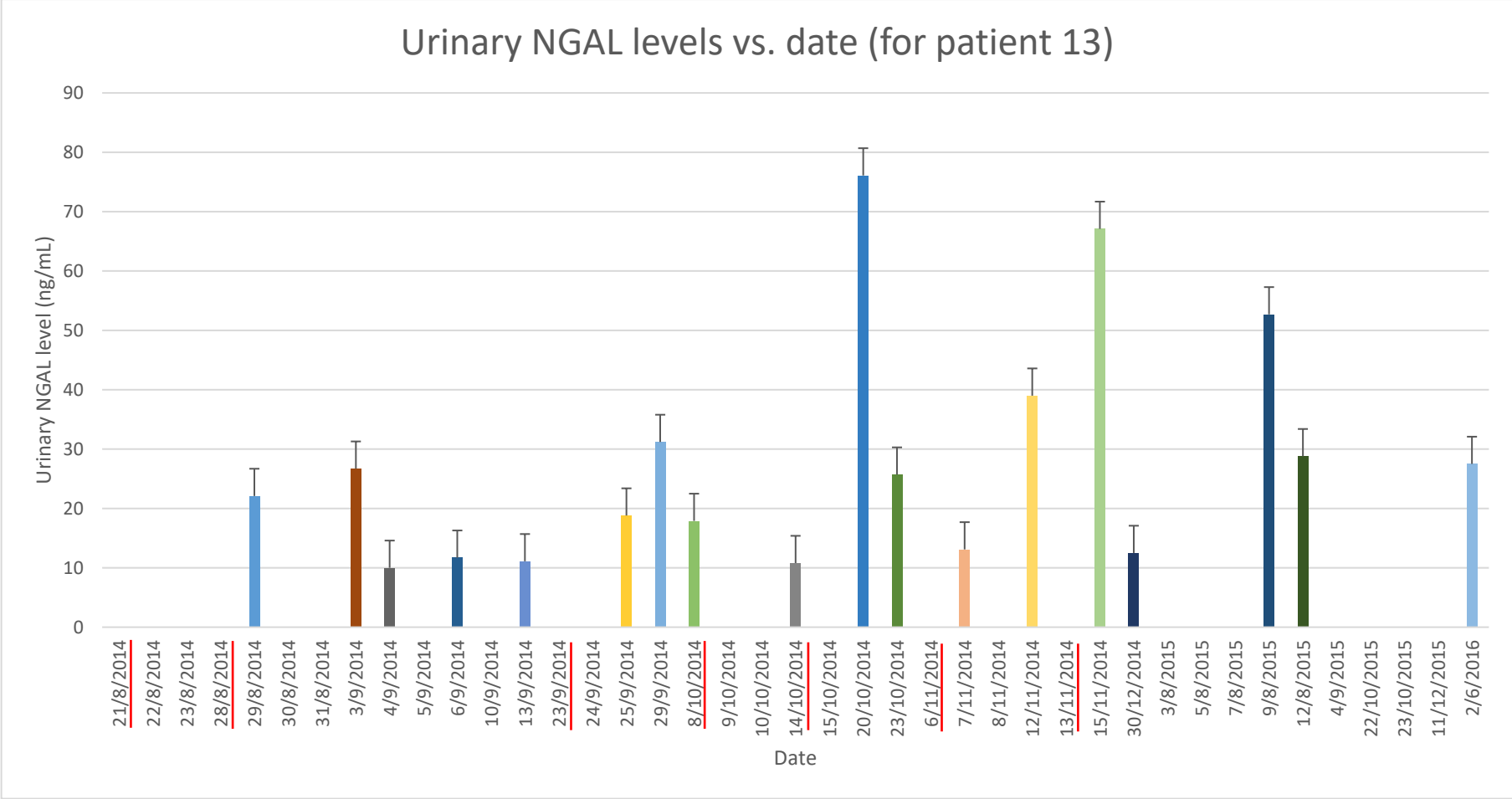


According to the data above (which disregards the data attained from patients 1 and 13), there is a general downwards trend in mean urinary NGAL levels as successive cisplatin cycles are given to patients, and then a sudden spike towards the 5th successive cycle of cisplatin.

5.3.2.5. Urinary NGAL levels vs. date

Data regarding urinary NGAL levels vs. date (for each patient) has been analysed, where there does not seem to be an apparent correlation between induction of cisplatin and an increase in NGAL levels. However, for some patients (5, 6, 13, 14, 15, 18), there are points of increase in urinary NGAL levels after cisplatin administration, however, these data points are not consistent within the individual patient and the cohort. Nevertheless, data relating to an explained patient (patient 13) will be presented in the respective figure below (***Figure 13***) where red vertical lines on the x-axis of these charts indicate when cisplatin was administered. Other individual patient graphs (patients 5, 6, 14, 15 and 18) will be contained within ***Appendix 5***.

Figure 13. Urinary NGAL levels vs. date (for patient 13)

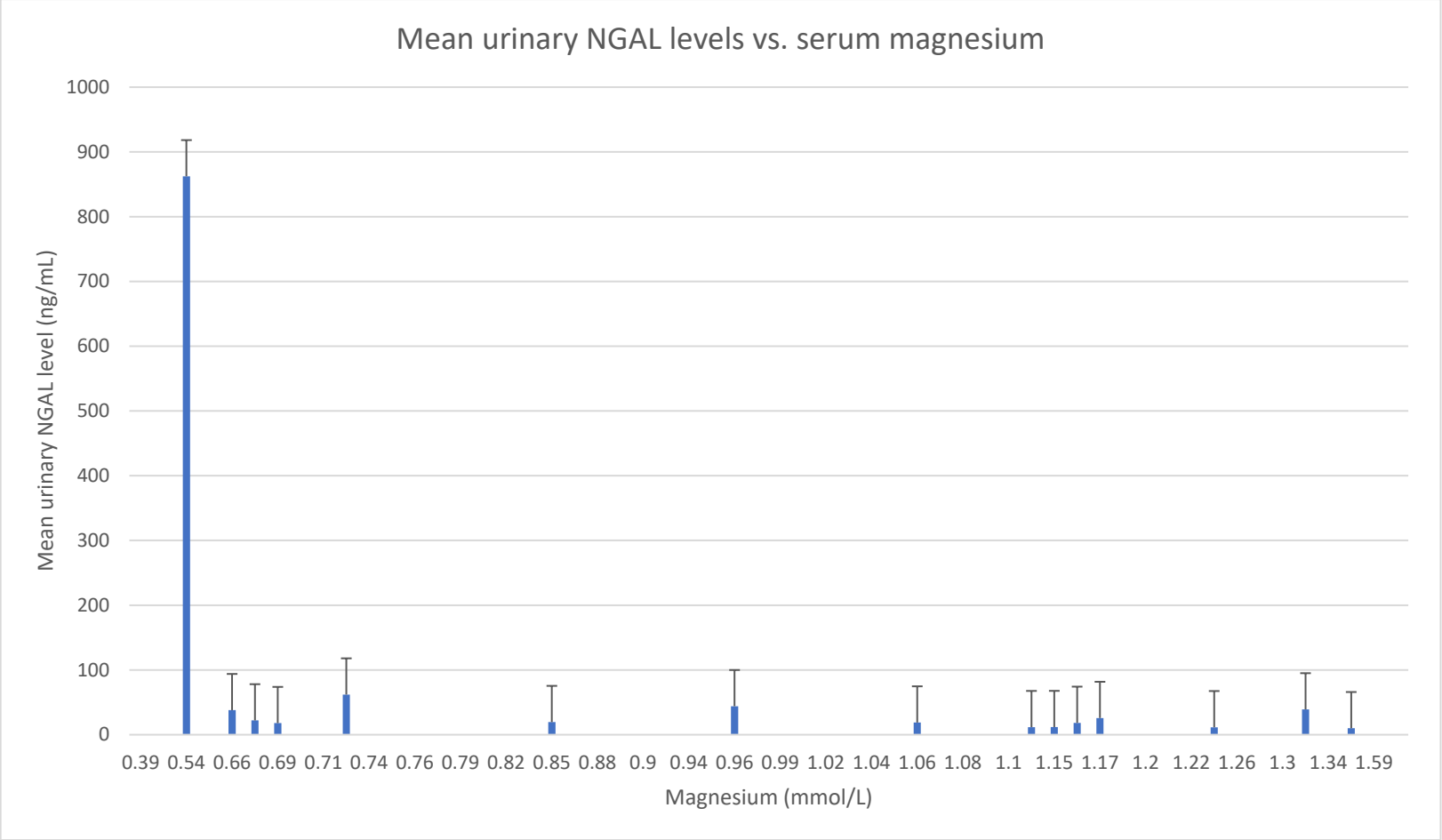


*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

5.3.2.6. Mean urinary NGAL levels vs. urine and serum biochemistry

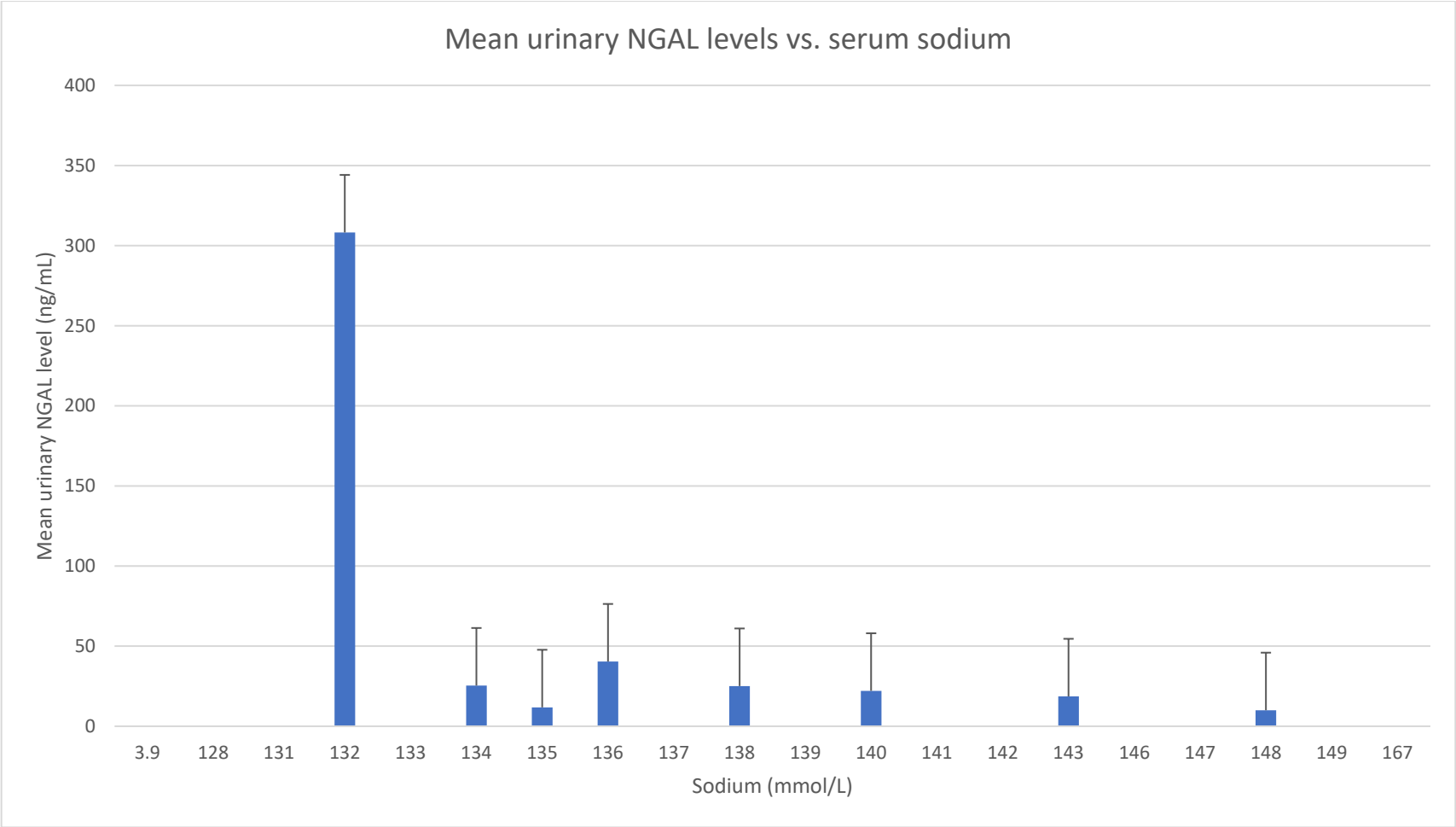
Data regarding mean urinary NGAL levels vs. serum and urinary biochemistry has been analysed, where the mean urinary NGAL levels was highest outside of the normal range for three out of eight serum biochemistry tests (magnesium, sodium and albumin). Although data regarding urinary biochemistry will be contained in ***Appendix 6***, these results were not accompanied with normal ranges and there does not seem to be a general consensus on what the "normal" range is for these urinary biochemistry tests, especially in a paediatric population. Nevertheless, data regarding the 3 serum biochemistry tests (magnesium, sodium and albumin) will be presented in the respective figures below (***Figure 14***, ***Figure 15*** and ***Figure 16***), where other individual serum biochemistry graphs will be contained in ***Appendix 7***.

Figure 14. Mean urinary NGAL levels vs. serum magnesium



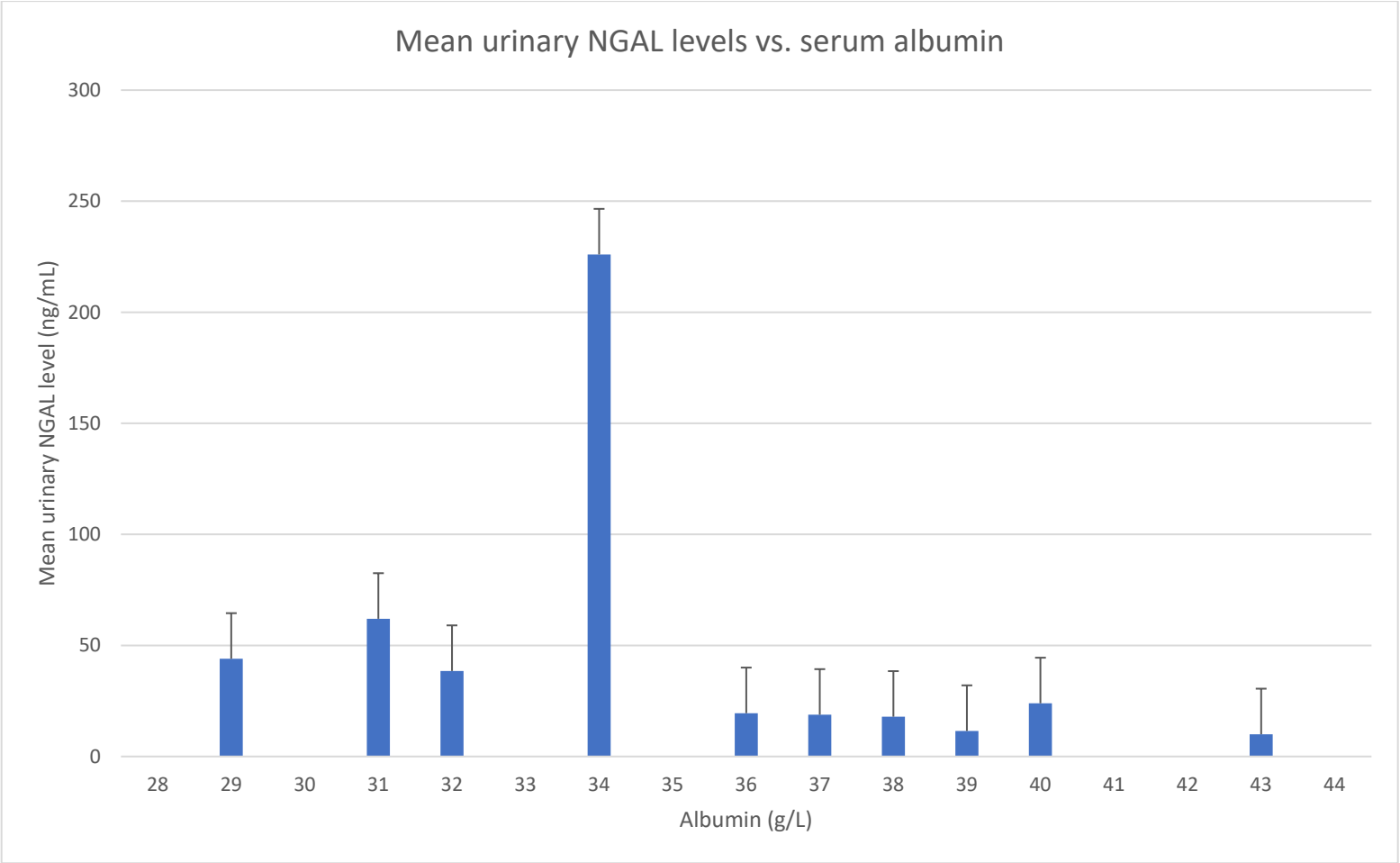
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 15. Mean urinary NGAL levels vs. serum sodium



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 16. Mean urinary NGAL levels vs. serum albumin



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

5.4. Discussion

This is a study that evaluates the effectiveness of using the biomarker urinary NGAL for the early detection of cisplatin-induced AKI. According to analysed data contained within the results section, there does not seem to be a significant correlation between a rise in urinary NGAL and cisplatin use, with "baseline" (day 1) data often having higher urinary NGAL levels than any other days of the patient's cisplatin cycle. Furthermore, all patients that had detectable levels of mean baseline urinary NGAL scored a normal p-RIFLE grade (based on creatinine criterion) and most patients (eight out of 11 patients) which had less than detectable levels of mean baseline urinary NGAL scored a normal p-RIFLE grade, whilst three patients with less than detectable levels of mean baseline urinary NGAL scored abnormal p-RIFLE grades (stage I), suggesting the lack of correlation between urinary NGAL and cisplatin-induced AKI. This is further supported with the analysis of "mean urinary NGAL levels vs. phases of cisplatin cycle" and "mean urinary NGAL levels vs. successive cisplatin cycles", where both analyses showed that baseline or 1st cisplatin cycle, respectively, had a higher mean urinary NGAL level than other phases/successive cycles. With regards to the correlation of urinary NGAL levels and conditions suffered by the cohort of patients, there does not seem to be any correlation, where osteosarcoma and medulloblastoma were present in both high baseline urinary NGAL and low baseline urinary NGAL groups.

Even after disregarding potentially anomalous data received from patient 1 (due to a significantly higher mean urinary NGAL level during their 3rd cycle of cisplatin compared to other patients) and patient 13 (as they were the only patient to experience a 6th cisplatin cycle) from the analysis of "mean urinary NGAL levels vs. successive cisplatin cycles", the results show a decreasing mean urinary NGAL level from the 1st cisplatin cycle to the 4th cisplatin cycle, where there is a spike in the 5th cisplatin cycle for which we do not have an explanation for. Although six patients out of the 21 patients were observed to show points of increase in urinary NGAL levels on certain dates (within the analysis of "urinary NGAL levels vs. date"), the overall results show that there is not a significant association with increase of NGAL after cisplatin induction.

Although animal studies have shown increased NGAL secretion in cisplatin-induced nephrotoxicity (207-209) and a rodent study has showed upregulation of proximal tubule NGAL expression after cisplatin administration (210), human studies are sparse (mainly only on adults), where many adult patients from these studies experienced elevated urinary NGAL levels before treatment (211-216), as we have experienced with the PINGU study and where we can see similarities between our results. However, one study (217) evaluated the effectiveness of the early detection of AKI through urinary NGAL within a paediatric population and reported that the baseline urinary NGAL levels amongst those taking cisplatin were not higher than the baseline urinary NGAL levels amongst those

taking the non-chemotherapy control, which directly contradicts our results. Additionally, another study (218) measured urinary NGAL levels amongst a cohort of 30 children with solid tumours that had cisplatin administered for their treatment, where researchers took urinary NGAL measurements two times, one week after the start of treatment and at the end of cancer treatment. With this study, NGAL levels correlated well with the identification of AKI for the "end of cancer treatment" NGAL measurements, however, there is uncertainty regarding whether the AKI had already developed prior to this measurement, thus being an ineffective "early" biomarker for the identification of AKI (218). Looking at the inconsistency of results regarding the effectiveness of NGAL in the identification of AKI amongst humans written above, these inconsistencies could be attributed to a variety of factors. Cisplatin can be used to treat a plethora of malignancies, where these patients can differ greatly with age, risk factors and morbidities, furthermore, there may be unknown factors that affect urinary NGAL concentrations during cisplatin use (217). There is also a suggestion that a more severe injury phenotype can be required for the observation of elevated biomarkers when concerning cisplatin-induced nephrotoxicity (217). However, when concerned with our study (PINGU), we deem that there was not a significant association between NGAL concentrations and cisplatin-induced AKI, especially as an early detector of AKI.

Our results have shown that urinary NGAL levels are more likely to rise during non-AKI episodes compared to AKI episodes, where another study (that measured urinary biomarkers of adults treated with cisplatin) has observed the same phenomenon within their cohort (219). This could be due to lack of subclinical renal injury with cisplatin-induced nephrotoxicity, which is especially relevant to this population, considering that paediatric patients receive a large amount of fluids, impairing the ability to measure serum creatinine effectively and therefore leading to serum creatinine concentration dilution, where this theory aligns with scientific consensus that biomarkers like NGAL can be useful for the detection of subclinical AKI (220). In support of the previous point addressed, only five out 12 patients had pre-dose GFRs that were lower than normal range, with the majority of patients within our cohort having normal/high pre-dose GFRs measured, this could be due to the large amount of fluid administered before cisplatin treatment, leading to serum creatinine concentration dilution. Although not observed within our study, some studies (217, 221, 222) have reported that paediatric patients with AKI can have larger pre-dose GFRs than paediatric patients without AKI, where this could be due to these patients having a lower muscle mass and therefore, being at a higher risk of AKI.

Although we did collect serum and urine biochemistry samples to characterise nephrotoxicity, mean urinary NGAL levels were the highest within abnormal range for three out of eight serum biochemistry tests (sodium, magnesium, and albumin), however, for both values that scored the

highest mean urinary NGAL for sodium (132 mmol/L, 135-145 mmol/L) and albumin (34 g/L, 37-53), these values were marginally off from their "normal" respective ranges. Although our results do not signify the effectiveness of NGAL in detecting cisplatin-induced AKI (when concerning our serum biochemistry samples), the scientific consensus on the definition of AKI relies mainly with the evaluation of serum creatinine rise, where tubular injury measures (e.g. hypophosphatemia) should be included to aid in the definition of cisplatin-induced nephrotoxicity (217, 223).

5.4.1. Limitations and recommendations for future studies

Some limitations within our study must be noted. Our study had a small sample size, where most patients provided multiple urinary NGAL samples. Due to our sample size, our ability to control confounders (e.g., type of malignancy) was impaired. As with the structure of collection of NGAL levels within the PINGU study, we were not able to discern the correlation of urinary NGAL levels with prior exposure of chemotherapeutic drugs and "recovery" between chemotherapy cycles, where this a major area for future research for the understanding of how NGAL levels can differ with prior exposure of chemotherapy and the "recovery" phase between cisplatin cycles. Although our study did not find that "younger" patients were associated with higher urinary NGAL levels, which has been shown in other studies (217, 224), this would suggest for future studies to emphasise and control for age, when concerning the evaluation of urinary NGAL for the detection of cisplatin-induced nephrotoxicity. Our study did not include a control group, which would help our understanding of what are "normal" NGAL values. Furthermore, our study did not place an emphasis with the dosing of the chemotherapy administered and specific drug treatment protocols, where these confounders may have a significant impact on the relationship between urinary NGAL and chemotherapeutic-induced nephrotoxicity, and an avenue that future research should focus on.

Judging from the lack of conclusive effectiveness of urinary NGAL at the detection of cisplatin-induced AKI, future studies should focus on studying new AKI biomarkers in the paediatric oncology population to see if previous biomarker research applies to this population and to find the most applicable way to use these biomarkers in clinical practice. Furthermore, these biomarkers need to be validated by being studied in larger paediatric populations, where more variables can be controlled, as some of these variables can significantly affect biomarker concentration. Another area of research paramount to this topic is the understanding of how drugs can mitigate chemotherapeutic-mediated AKI and how this affects biomarker levels, as there are a number of studies (107, 221, 225-227) that show the drugs can aide in the mitigation of chemotherapeutic-mediated nephrotoxicity. However, this can be a challenge as the paediatric oncology population is associated with complexity, where some drugs can promote tumour growth and cause additional side-effects/adverse events.

5.5. Conclusion

Although the literature is mixed, data from our study does not support urinary NGAL for use as a potential biomarker of cisplatin-induced nephrotoxicity, larger studies may help improve this picture to provide evidence for urinary NGAL and other biomarkers to potentially impact the way we diagnose and treat chemotherapeutic-mediated nephrotoxicity. We strongly advocate the further research into biomarkers with larger paediatric oncology populations, which are more able to control confounders and other variables, allowing a more accurate evaluation of these biomarkers. Additionally, studies regarding drug interactions with urinary NGAL will help further elucidate how these biomarkers work and ultimately, how effective they can be within clinical practice.

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6. Appendices

6.1. Appendix 1

ALDER HEY CHILDREN'S NHS FOUNDATION TRUST

The Prospective Investigation into urinary NGAL Utility in Paediatric Oncology Patients

PINGU Project

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Version 3.0 Dated 1st March 2012

Introduction and rationale

Although there has been a steady improvement in the survival of children with cancer, treatment for childhood malignancy remains associated with a significant risk of short, medium and long-term side effects. A number of chemotherapeutic agents in routine use are associated with nephrotoxicity that in the short term may produce significant acute renal damage, both glomerular and tubular, and in the long term may be associated with long standing renal problems. Tubular damage associated with chemotherapy frequently results in deficiency of magnesium, potassium and phosphate resulting in the need for prolonged electrolyte supplementation and on occasions problems such as hypophosphatemic rickets.

There is clearly a need for new markers of nephrotoxicity in patients receiving nephrotoxic chemotherapy so that significant renal damage can be identified and managed as early as possible and also so that further damage can be limited, for example by the avoidance of concomitant nephrotoxic drugs such as aminoglycoside antibiotics.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) appears to be an appropriate marker of renal damage to investigate in children receiving nephrotoxic chemotherapy. NGAL is responsible for the growth and differentiation of the renal tubular epithelial cells and exerts bacteriostatic effects in the distal urogenital tract by altering the bacterial siderophore-mediated iron acquisition [1]. The siderophore-iron-complex NGAL limits proximal tubular damage and reduces apoptosis. NGAL is normally expressed at very low levels in several human tissues, including kidney, lungs, stomach and colon [2]. Kidney epithelia express and excrete large quantities of NGAL into the urine when damaged by ischaemia-reperfusion injury, nephrotoxins, sepsis and chronic progressive changes [3]. NGAL has been identified as the protein with the earliest rise and peak after renal ischaemia [3-4]. NGAL seems to be an early biomarker in contrast to the currently available laboratory markers of renal damage used in everyday clinical practice.

Urinary NGAL has been identified as a potential early marker of renal injury in children experiencing the following kidney insults; after cardiopulmonary bypass [5], sepsis in critical illness [1], delayed graft function in renal transplantation [6], contrast-induced nephropathy [7], haemolytic-uraemic syndrome [8] and lupus nephritis flares [9].

To date, information on NGAL as an early marker of renal damage in children receiving nephrotoxic chemotherapy is very limited. There appears to be only one previous publication of the utility of NGAL in patients receiving nephrotoxic chemotherapy. In this small study of 12 adults, urinary NGAL levels increased significantly more in patients receiving cisplatin, who subsequently developed AKI, than in controls at up to 15 days after cisplatin and the NGAL increase at day 2 after cisplatin predicted acute kidney injury (>25% serum creatinine increase vs. baseline) [10].
Nephrotoxicity associated with antibiotics, administered to children already receiving nephrotoxic chemotherapy, is another challenge facing paediatric oncologists. Many centres (including Alder Hey) use aminoglycosides as first line antibiotics for treatment of febrile neutropenia episodes. As many as 10-25% of therapeutic courses of aminoglycosides are complicated by nephrotoxicity, despite close patient monitoring [12].

There is a clear need for an early marker of kidney injury in this group of patients, so potentially further damage could be prevented by replacing aminoglycosides with non-nephrotoxic antibiotics if possible. We haven't identified any studies on the utility of NGAL in this setting.

NGAL levels have also been found to be elevated in various types of adult-type cancers including adenocarcinomas of the breast, bowel and urothelial carcinomas [14, 15]. There are no reports on NGAL levels in paediatric–type cancers apart from brain tumours including medulloblastoma, where urinary NGAL has been found to be elevated [16].

Objectives of the study

- To determine the utility of NGAL in predicting acute kidney injury (AKI) in paediatric oncology patients at risk of renal damage.
- To correlate urinary and blood measurements of NGAL in a group of patients within our cohort. The current Abbott assay has been sufficiently validated for use on urine, but in all of the situations described above, blood is routinely collected. We would therefore be able to use the assay to measure plasma NGAL that may contribute towards validating the assay with blood as opposed to urine in certain situations (e.g: a young infant who may be unable to produce a urine sample within a timely manner or on demand).
- To lead to future studies that may allow the investigation into the effect that early intervention would have on improving the renal outcome for these patients. This would require a randomised controlled trial of NGAL guided management versus standard management to show this effect. It is hoped that results from this initial study may prompt such future studies.

This initial project will allow us to gain the necessary experience of collecting samples and interpreting the levels of urinary NGAL with the clinical information available, whilst broadening its use within a paediatric setting in the UK. The confirmation of the utility of NGAL as an early marker of AKI could allow alternative strategies to be employed in the future, which might further limit kidney damage, for example: reducing or avoiding nephrotoxic medications and administering more fluids.

This study is a part of "The PINGU Project" – The Prospective Investigation Into NGAL Utility, which is being conducted at Alder Hey Children's NHS Foundation Trust in Liverpool.

As plasma and urinary NGAL levels have been reported to be elevated in certain conditions including sepsis, brain tumours or Down's syndrome and some of the patients enrolled into the study will fall into one of these categories, we are aiming to measure baseline NGAL levels prior to the start of nephrotoxic therapy and then compare it with subsequent levels when patients are exposed to nephrotoxic agents.

We are going to use RIFLE criteria for kidney injury, which are as follows:

stage I (Risk): increased creatinine x1.5 or GFR decrease >25% or urine output <0.5ml/kg/h x 6hr

stage II (Injury): increased creatinine x 2 or GFR decrease > 50% or urine output <0.5ml/kg/h x 12hr

stage III (Failure): increased creatinine x 3 or GFR decrease > 75% or urine output <0.3ml/kg/h x 24hr or anuria x 12hr [17].

Patient selection criteria

The study will include 2 groups of patients:

I. Patients receiving nephrotoxic chemotherapy

Eligibility:
1. Patients receiving one or more of the following nephrotoxic drugs:
   - Cisplatin
   - Ifosfamide
   - high dose Methotrexate
2. Informed written consent.

Exclusions:
1. Urinary tract infection

II. Patients receiving nephrotoxic chemotherapy and receiving aminoglycosides

Eligibility:
1. Patients receiving Cisplatin, Ifosfamide or high dose Methotrexate up to 4 weeks prior to admission and receiving aminoglycosides on current admission.
2. Informed written consent.

Exclusions:
1. Urinary tract infection.

Diagnostic investigations during the study

I. Patients receiving nephrotoxic chemotherapy

1. **Urinary NGAL (uNGAL):**
   - prior to chemotherapy (baseline)
   - daily until the end of administration of nephrotoxic chemotherapy
   - at the first clinic appointment after the end of treatment, 6 and 12 months after the end of treatment

2. **Serum NGAL (sNGAL):**
   - prior to chemotherapy
   - daily until the end of administration of nephrotoxic chemotherapy
   - at the first clinic appointment after the end of treatment and 12 months after the end of treatment

3. '**Oncology Profile'** (urea, creatinine, sodium, potassium, bicarbonate, anion gap, magnesium, calcium, phosphate):
   - prior to chemotherapy
   - daily until the end of administration of nephrotoxic chemotherapy
   - at the first clinic appointment after the end of treatment and 12 months after the end of treatment

4. **Urine Biochemistry** - urine dipstick (blood, protein, glucose), urine albumin/creatinine ratio, retinol binding protein (RBP), phosphate, calcium, creatinine.
   - prior to chemotherapy
   - daily until the end of administration of nephrotoxic chemotherapy (except for
   - phosphate, calcium and creatinine – only on the last day of chemotherapy)
   - at the first clinic appointment after the end of treatment, 6 and 12 months after the end of treatment

5. **GFR** (Cr EDTA excretion)
   - before alternate courses of chemotherapy
   - at the end of chemotherapy

II. Patients given nephrotoxic chemotherapy and receiving aminoglycosides.

1. **Urinary NGAL (uNGAL):**
   - prior to 1st dose of aminoglycosides
   - daily for 4 days

2. **Serum NGAL (sNGAL**):
   - prior to 1st dose of aminoglycosides
   - daily for 4 days

3. '**Oncology Profile'** (urea, creatinine, sodium, potassium, bicarbonate, anion gap, magnesium, calcium, phosphate and liver function tests) and uric acid:
   - prior to 1st dose of aminoglycosides
   - from 1 to 4 times a day for 4 days

4. **Urine Biochemistry** - urine dipstick (blood, protein, glucose), urine albumin/creatinine ratio, RBP, phosphate, calcium and creatinine:
   - prior to 1st dose of a*minoglycosides*
   - daily for 4 days (except for phosphate, calcium and creatinine – only on day 4)

Clinical observations and drug therapy

I. Patients receiving nephrotoxic chemotherapy
1. Height and weight on admission.
2. Daily fluid balance if on i.v. hydration.
3. Daily blood pressure (the highest and the lowest measurement if more then one taken daily).
4. The number of courses of aminoglycosides (gentamicin or amikacin) in the last 6 months.
5. The number of courses of nephrotoxic chemotherapy given and which of the 3 drugs were given.
6. The use of electrolyte supplementation on admission (supplement and dose).

II. Patients given nephrotoxic chemotherapy and receiving aminoglycosides
1. Height and weight on admission.
2. Daily fluid balance if on i.v. hydration.
3. Daily blood pressure.
4. The number of courses of aminoglycosides (gentamicin or amikacin) in the last 6 months.

5. The number of courses of nephrotoxic chemotherapy given and which of the 3 drugs were given
6. The use of electrolyte supplementation on admission (supplement and dose).

Sample Size
We aim to recruit patients over a period of one year. It is difficult to predict precisely the number of patients presenting with a particular diagnosis and thus receiving a particular protocol over a period of a year. In addition, the mode of administration of a particular nephrotoxic chemotherapy agent varies according to particular protocols.

Our best estimates of the number of patients to be included in the study are as follows:

I. Patients receiving nephrotoxic chemotherapy

- Osteosarcoma (cisplatin, HD MTX +/- Ifosfamide) - 3 patients/yr (total of 48 courses of nephrotoxic chemotherapy)
- Ewing's Sarcoma (Ifosfamide) 4 patients/yr (56 courses)
- Soft Tissue Sarcoma (Ifosfamide) 5 patients/yr (25 courses)
- Neuroblastoma (Cisplatin and high dose Carboplatin) 5 patients/yr (30 courses)
- Medulloblastoma (Cisplatin) 3 patients/yr (9 courses)
- Hepatoblastoma (cisplatin) - 1 patient/yr (6 courses),
- Rare/other tumours - 3 patients/yr (9 courses)

- The estimated total number of patients is 24 per year and 183 courses of nephrotoxic chemotherapy per year.
- The number of test sets per episode of nephrotoxic chemotherapy will range between 3 and 6 sets per episode of chemotherapy admission.
- Based on these figures it is estimated that around 750 test sets will be performed over one year for the study of acute nephrotoxicity.
- In addition a further 3 test sets will be performed as follow up over one year to determine delayed renal damage, which is 72 further tests.
- The estimate number of test sets in this group is thus 800.

II. Patients given nephrotoxic chemotherapy and receiving aminoglycosides.

- We plan to include 10 patients in this group, as a pilot study.
- The estimate number of test sets in this group is 40.

The total estimate number of patients entered into the entire study is thus 34 or less - as some patients may be entered into group I and group II.

Total estimate number of test sets for both groups of patients: 840.

Duration of the study – min 2 years:
- 1 year of the recruitment of new patients (group I, II)
- 1 year of follow up of patients receiving nephrotoxic chemotherapy (group I).

Further studies

Patient data may be reused and urine samples stored and reanalysed for additional, ethically approved research studies, provided separate consent is sought and provided by the patient and/or family.

Statistical analysis

Log rank tests will be used to assess whether NGAL concentrations are associated with the development of AKI. The Cox regression model will be used to explore these relationships after adjusting for possible confounding variables. It will allow us to predict the hazard (or risk) of outcomes for individuals given their prognostic variables. By dichotomising outcomes, we can calculate sensitivity, specificity, positive/negative predictive value, positive/negative likelihood ratios for NGAL for the diagnosis of AKI in our setting.

Receiver operator curves (ROC) will be constructed to explore possible thresholds for NGAL for the diagnosis of AKI. Analysis of NGAL in the control group will also help to confirm its specificity. The longitudinal changes of NGAL in relation to the time to development of AKI as well as time to resolution of AKI will be examined using joint modelling techniques [13].

Estimate costs of the study

Test Costs
The costs of NGAL testing (both urine and serum) will be covered by Abbott.
We will have to cover the costs of additional tests (which are not part of Oncology Unit routine practice) performed at the same timepoints as NGAL testing. The estimate number and cost of the tests is as follows:

Group I
1. "Oncology Profile" daily during the administration of nephrotoxic chemotherapy
   3 (4) days x 183 courses = ~ 750 tests x £6.70 = £5025
2. "Oncology Profile" 12 moths after the end of treatment
   1 x 24 patients = 24 tests x £6.70 = £161
3. Urine albumin/creatinine ratio during the administration of nephrotoxic chemotherapy
   3 (4) days x 183 courses = ~ 750 tests x £4.12 = £3090
4. Urine albumin/creatinine ratio at the end of treatment, 6 and 12 months after the end of treament.
   3 x 24 patients = 72 tests x £4.12 = £297
5. Urinary retinol binding protein during the administration of nephrotoxic chemothrapy
   3 (4) days x 183 courses = ~ 750 tests x £8 = £6000
6. Urinary retinol binding protein at the end of treatment, 6 and 12 months after the end of treatment
   3 x 24 patients = 72 tests x £8 = £576
7. Urinary phosphate, calcium and creatinine on the first and last day of nephrotoxic chemotherapy
   2 x 183 courses = 366 x £4.65 = £1702

Total test costs in group I ~ £ 16,852

Group II
1. Urine albumin/creatinine ratio during the administration of aminoglycosides
   4 days x 10 patients = 40 x £4.12 = £165
2. Urinary retinol binding protein during the administration of aminoglycosides
   4 days x 10 patients = 40 x £8 = £320
3. Urinary phosphate, calcium and creatinine on day 1 and 4 of antibiotic treatment
   2 days x 10 patients = 20 x £4.65 = £93

Total test costs in group II ~ £ 578

Total estimate costs for the whole study (group I and II): £ 17,430

Overheads: £ 2,344

Statistics:
Estimated cost: £6,569

Total estimate cost of the study: £ 26,343

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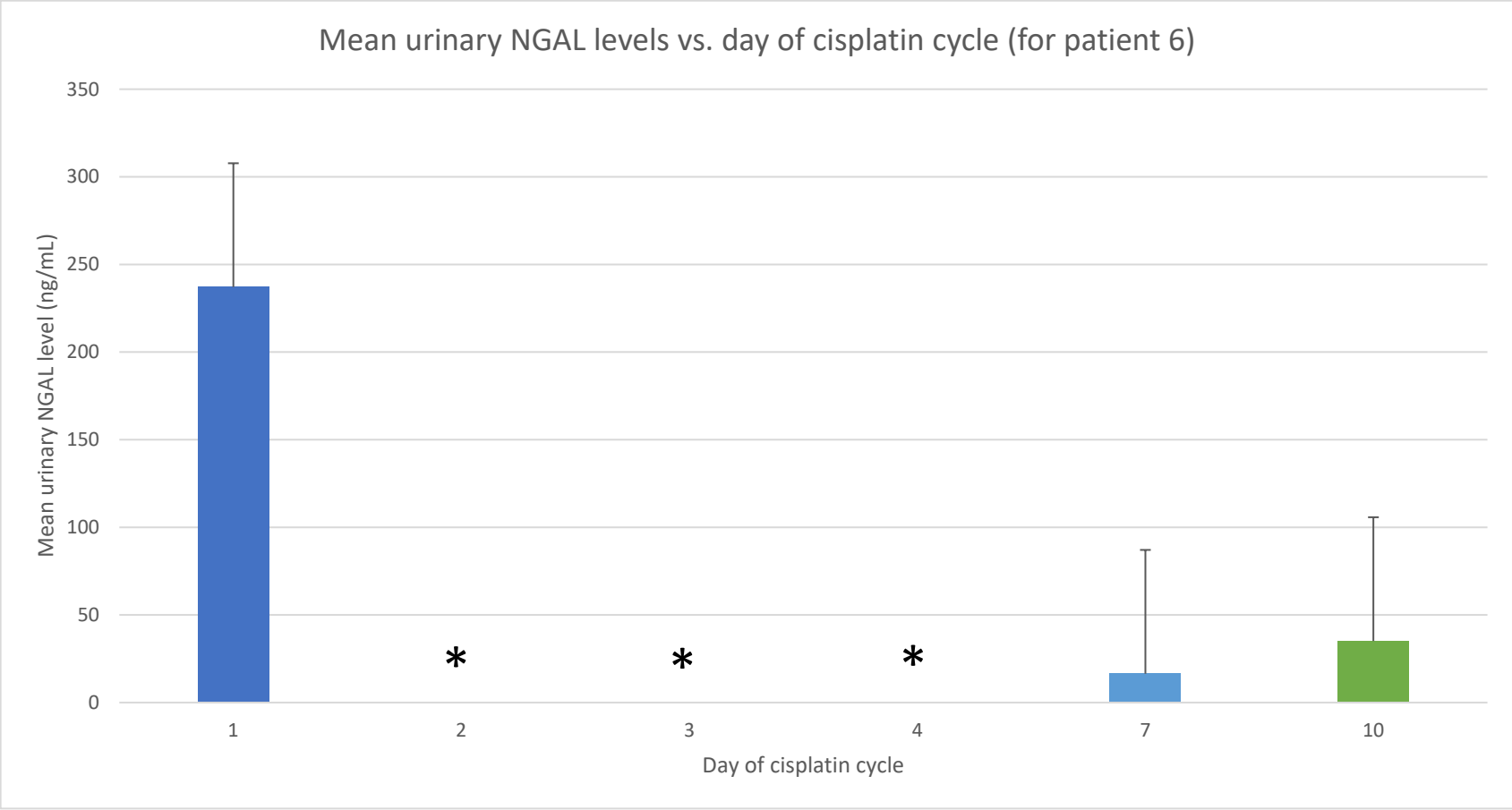
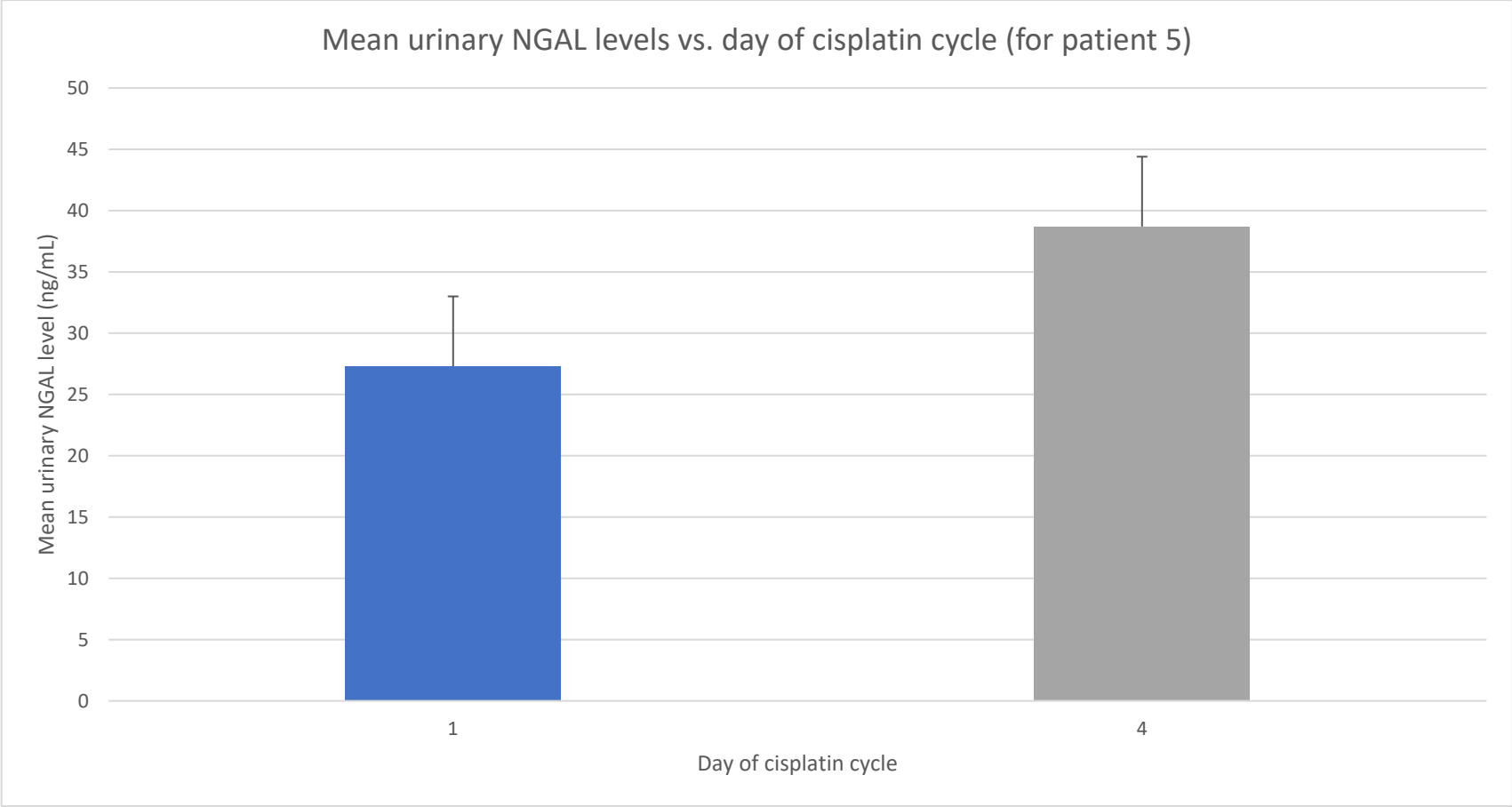
6.2. Appendix 2

Figure 17. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 6)



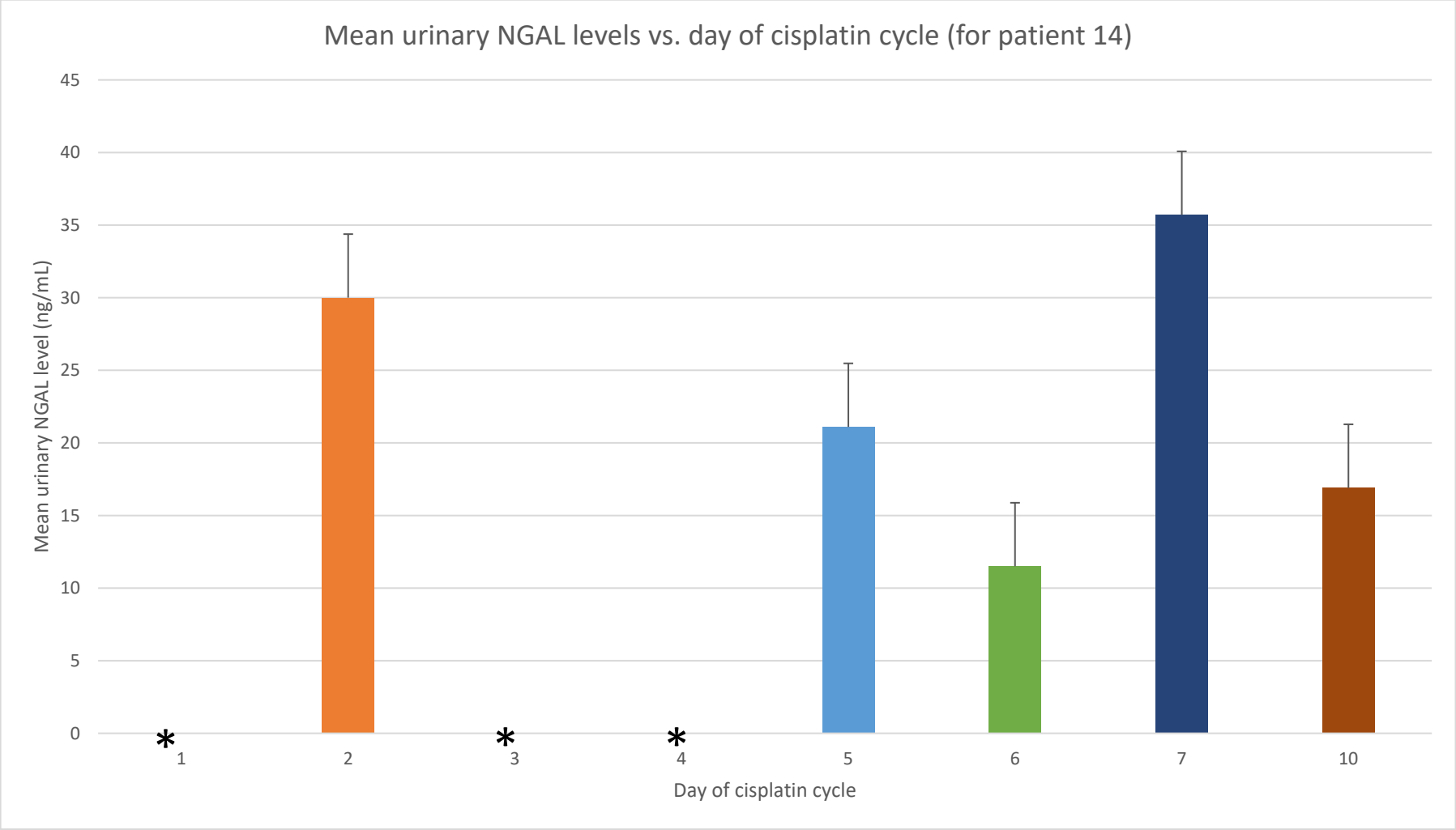
*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 18. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 5)



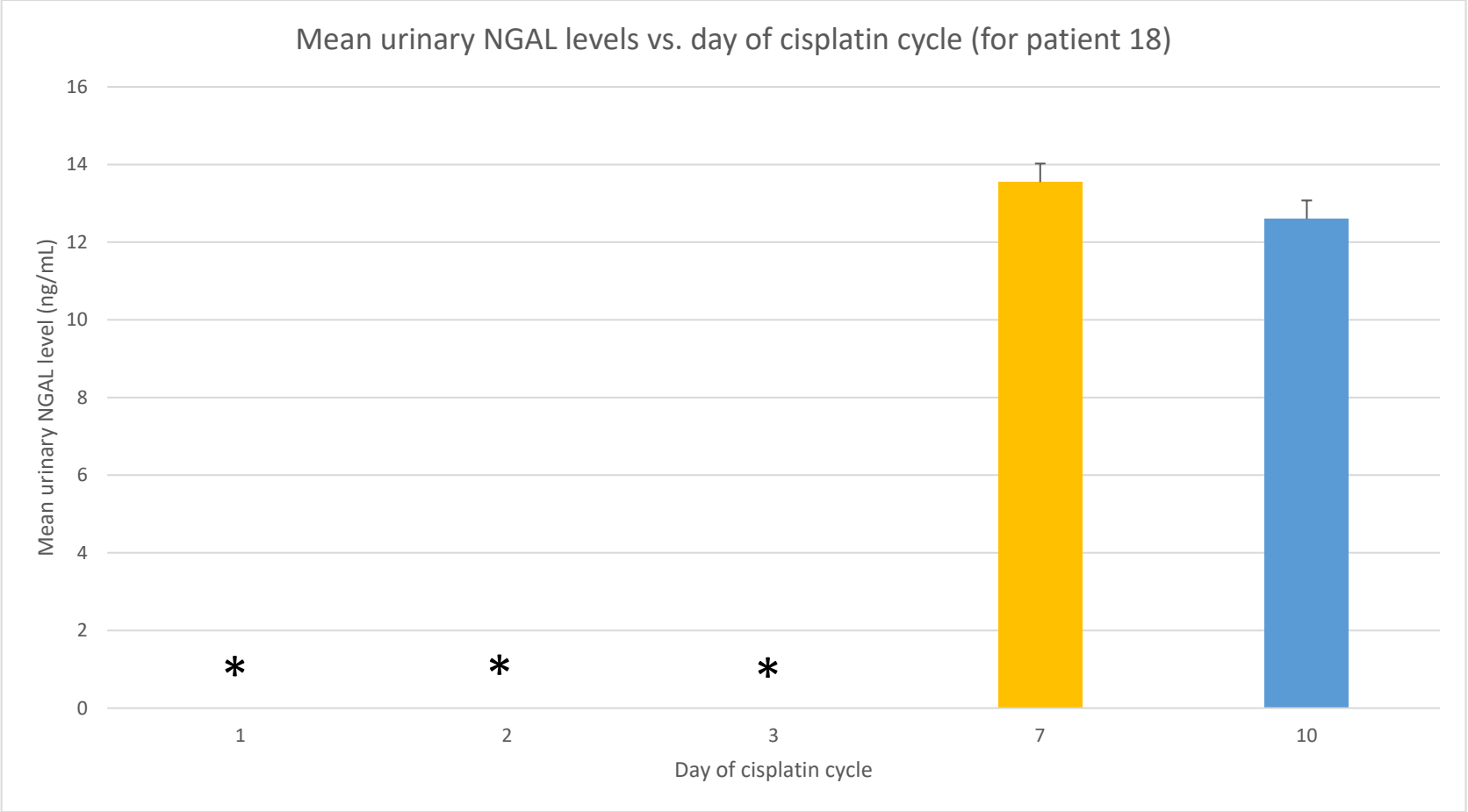
6.3. Appendix 3

Figure 19. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 14)



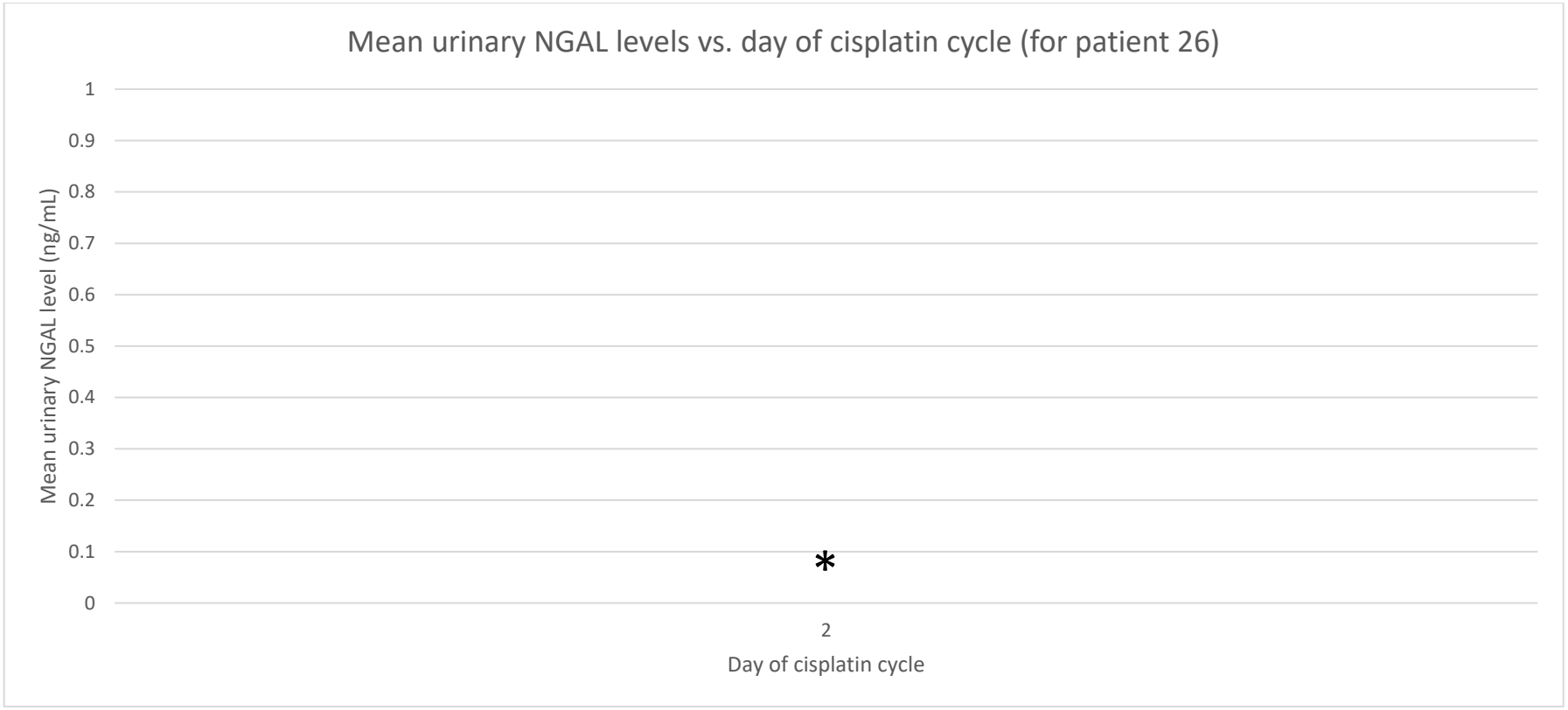
*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 20. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 18)



*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 21. Mean urinary NGAL levels vs. day of cisplatin cycle (for patient 26)



*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

6.4. Appendix 4

Figure 22. Mean urinary NGAL levels vs. phases of cisplatin cycles (for patient 5)

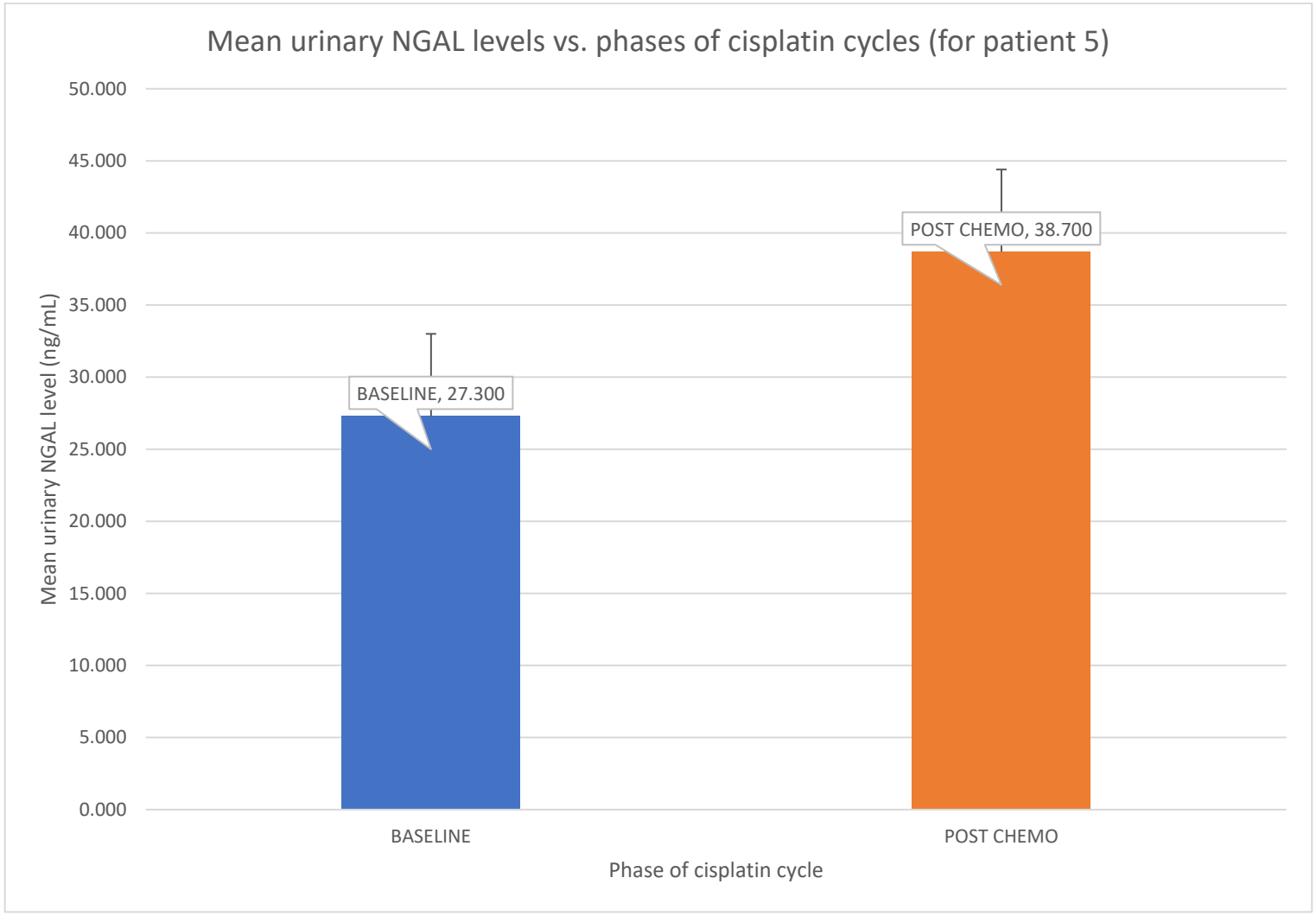
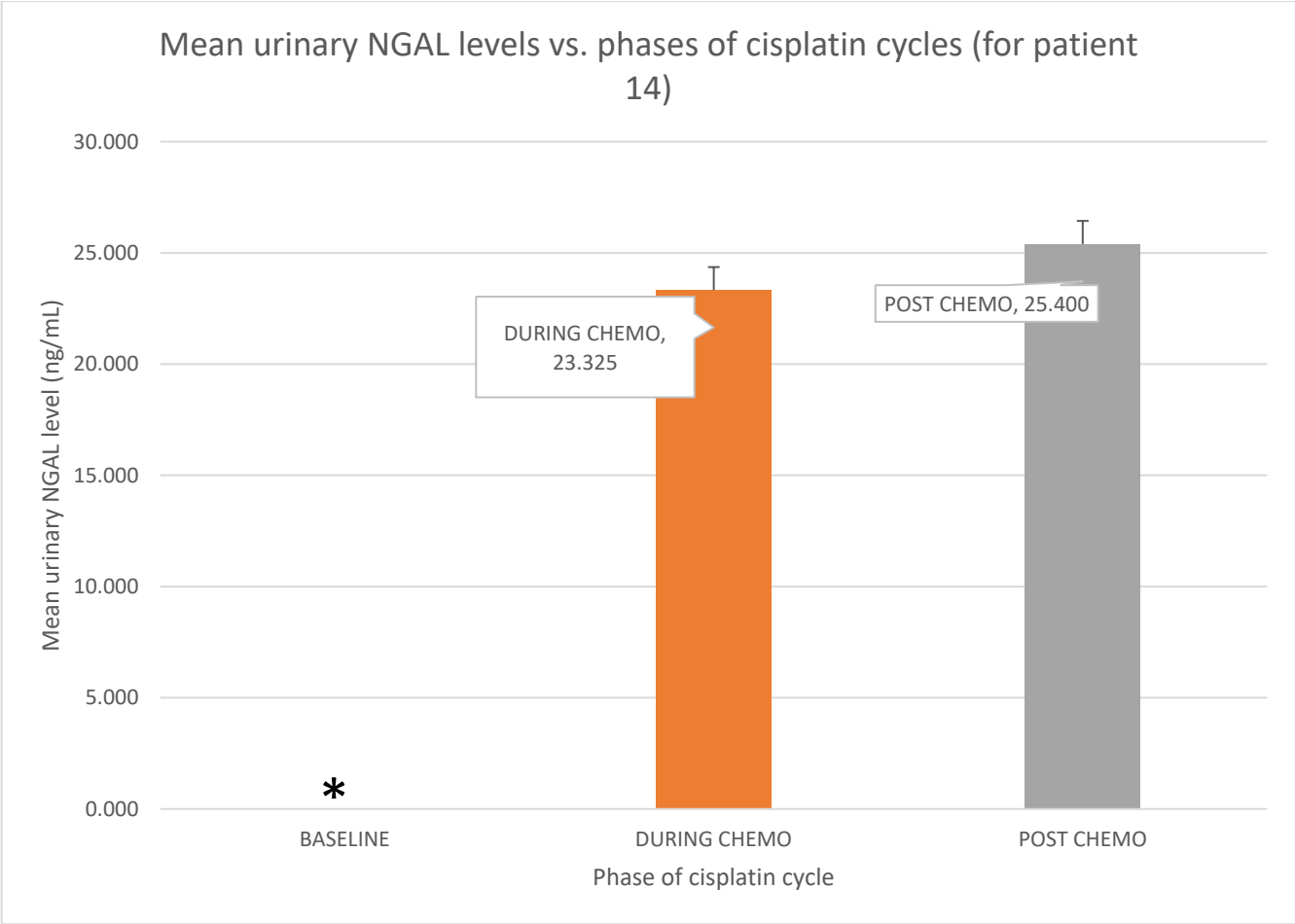


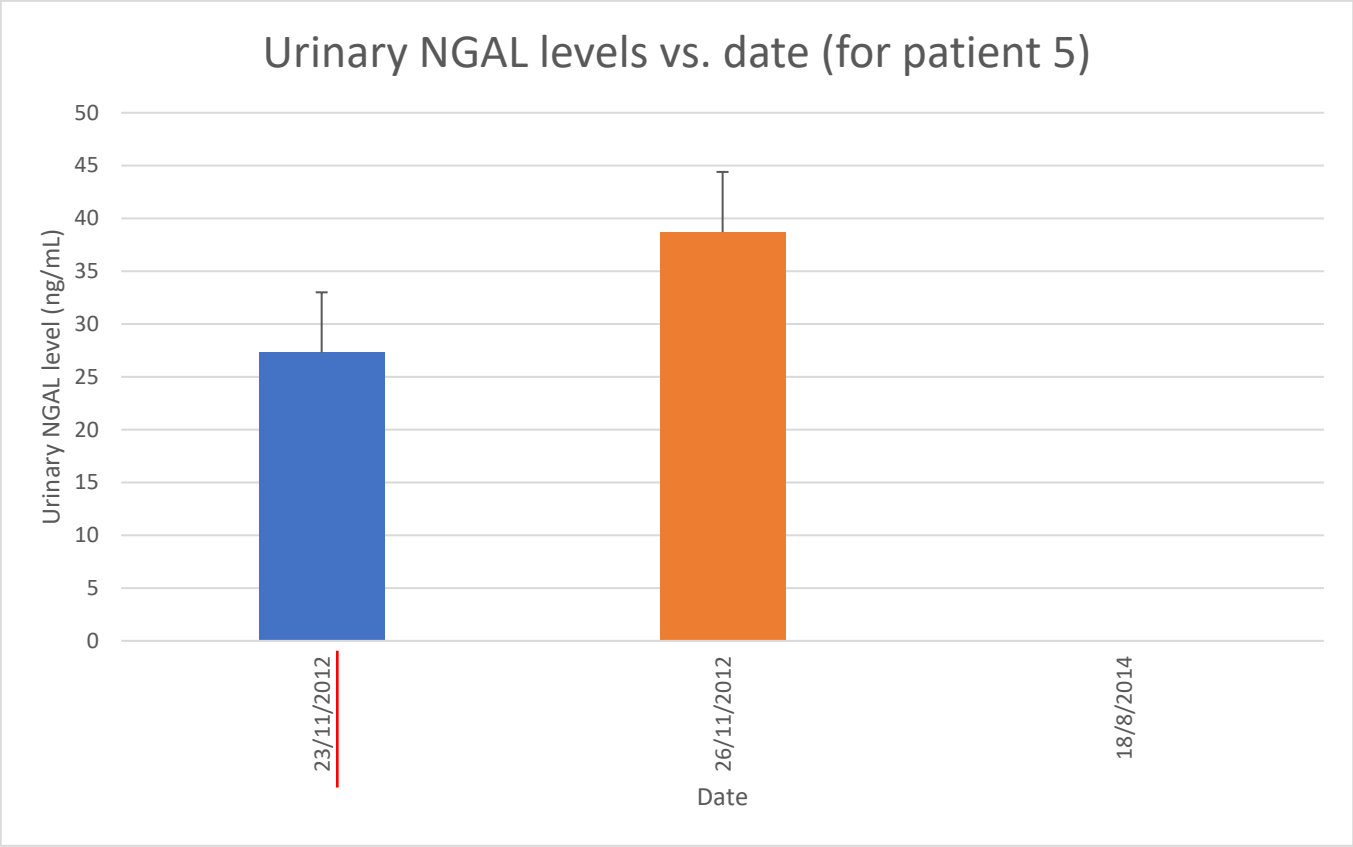
Figure 23. Mean urinary NGAL levels vs. phases of cisplatin cycles (for patient 14)



*Denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

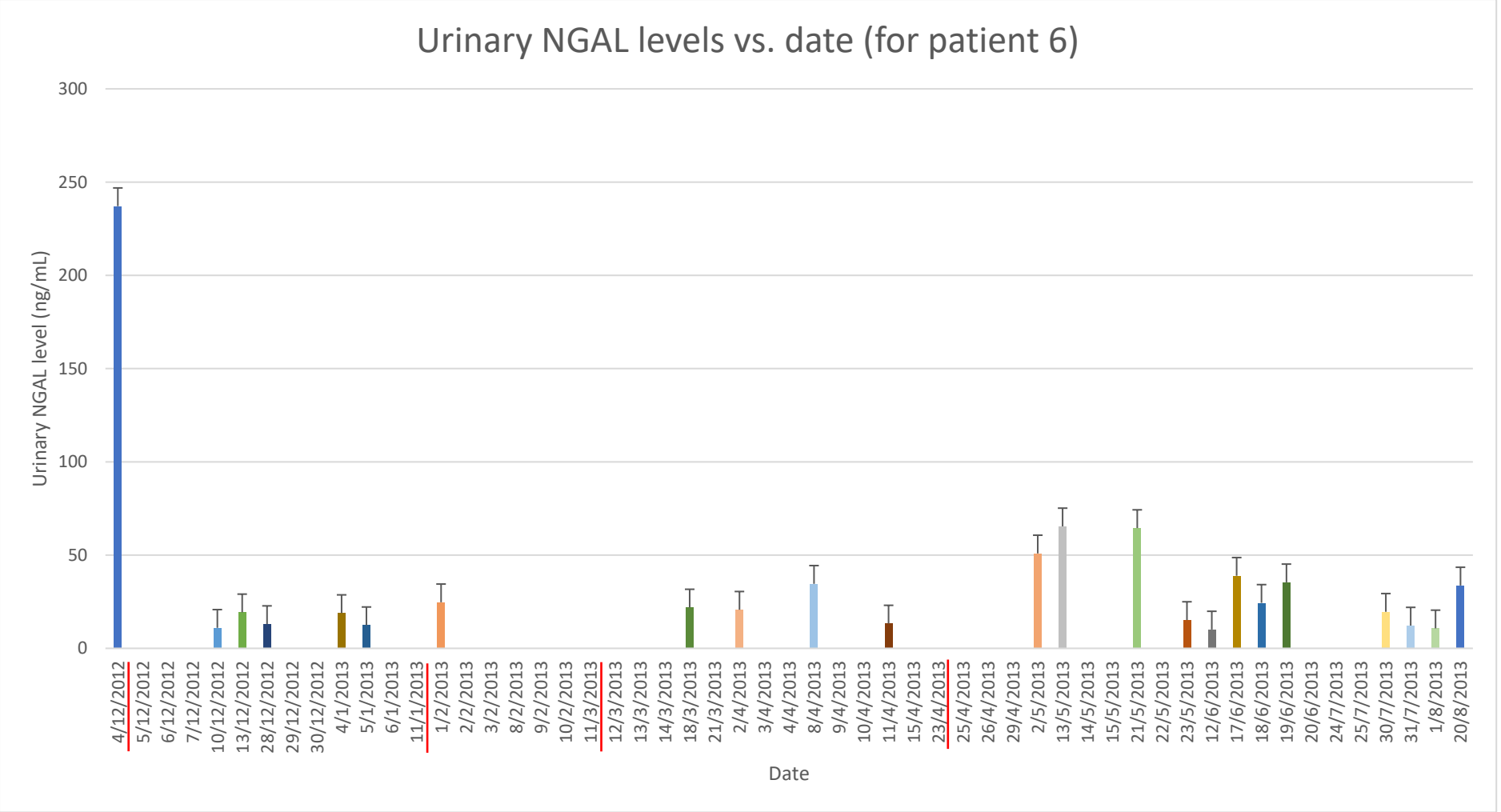
6.5. Appendix 5

Figure 24. Urinary NGAL levels vs. date (for patient 5)



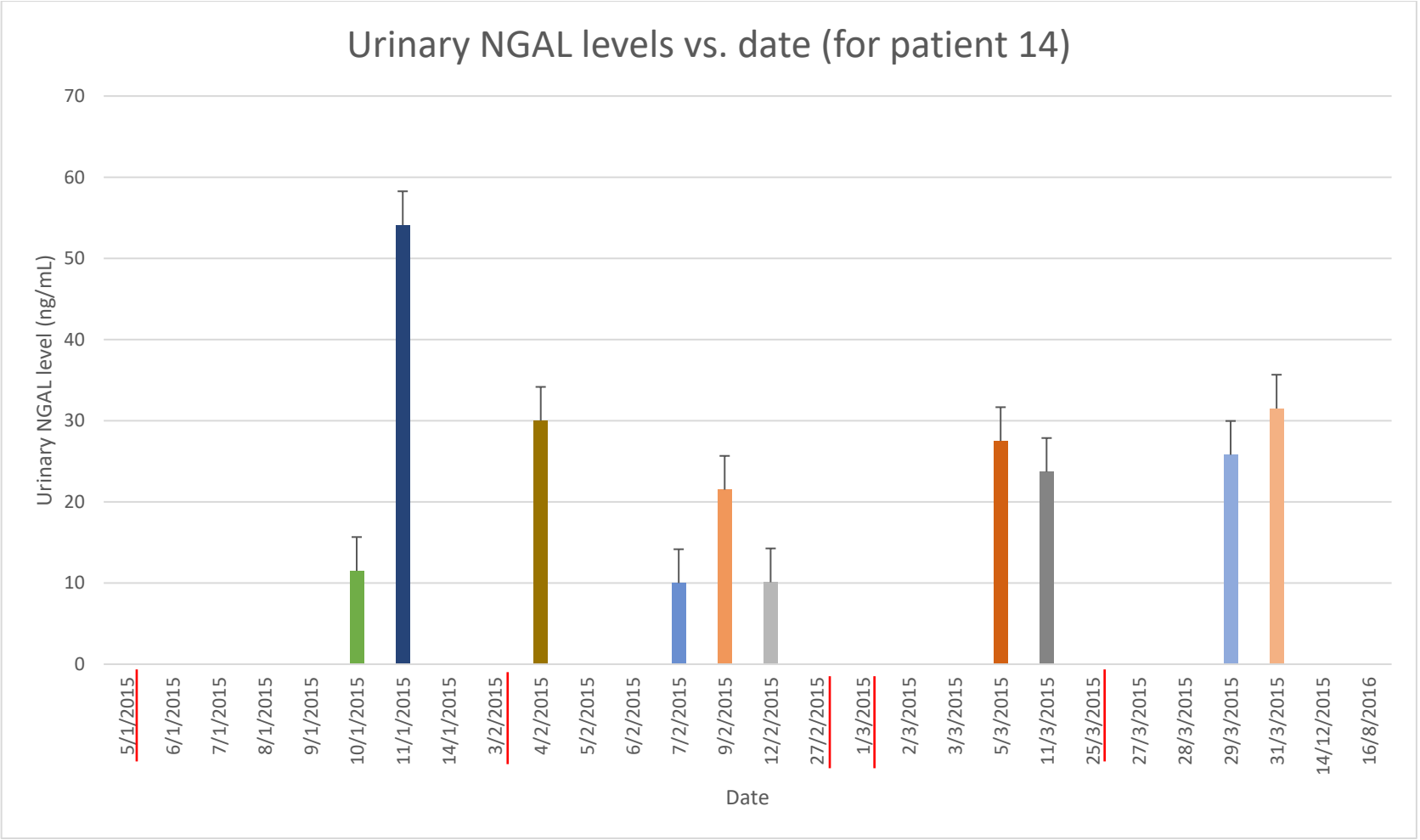
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 25. Urinary NGAL levels vs. date (for patient 6)



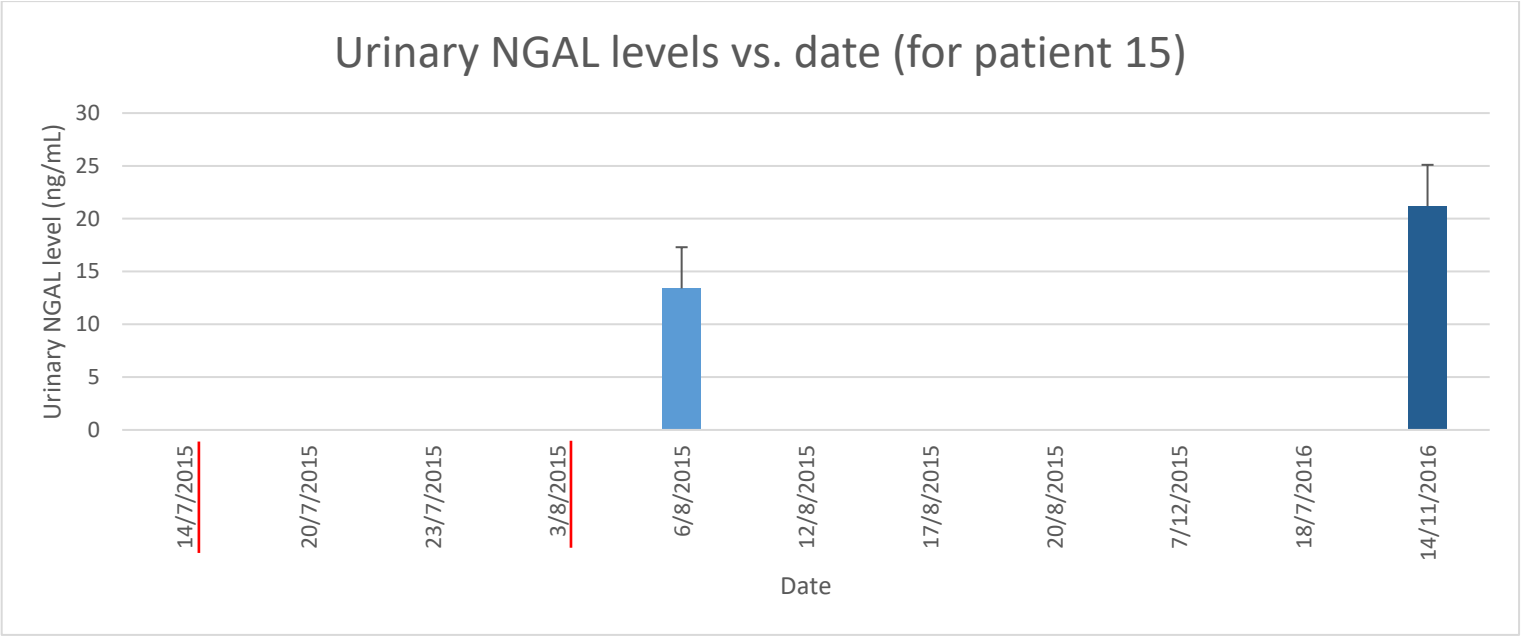
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 26. Urinary NGAL levels vs. date (for patient 14)



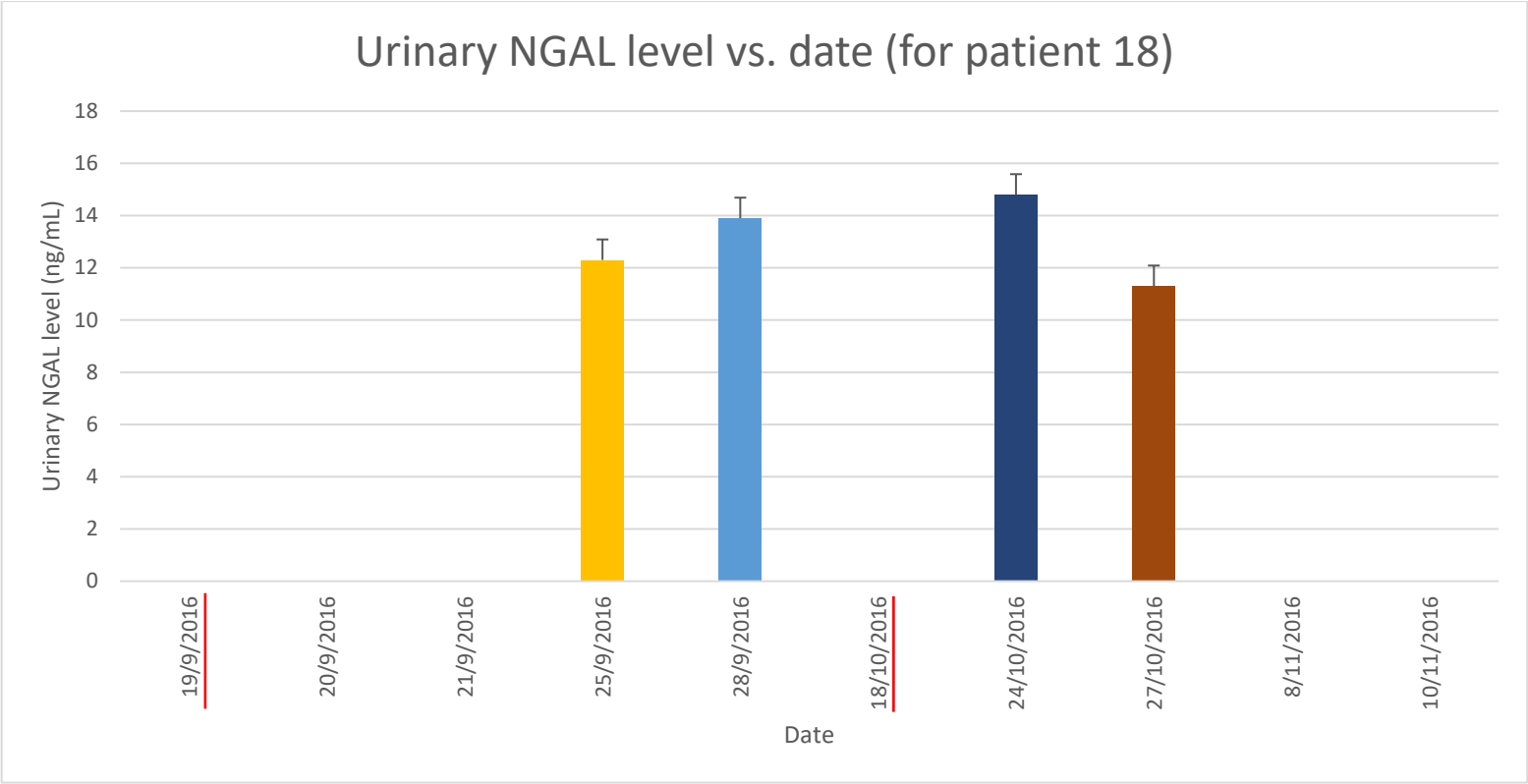
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 27. Urinary NGAL levels vs. date (for patient 15)



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

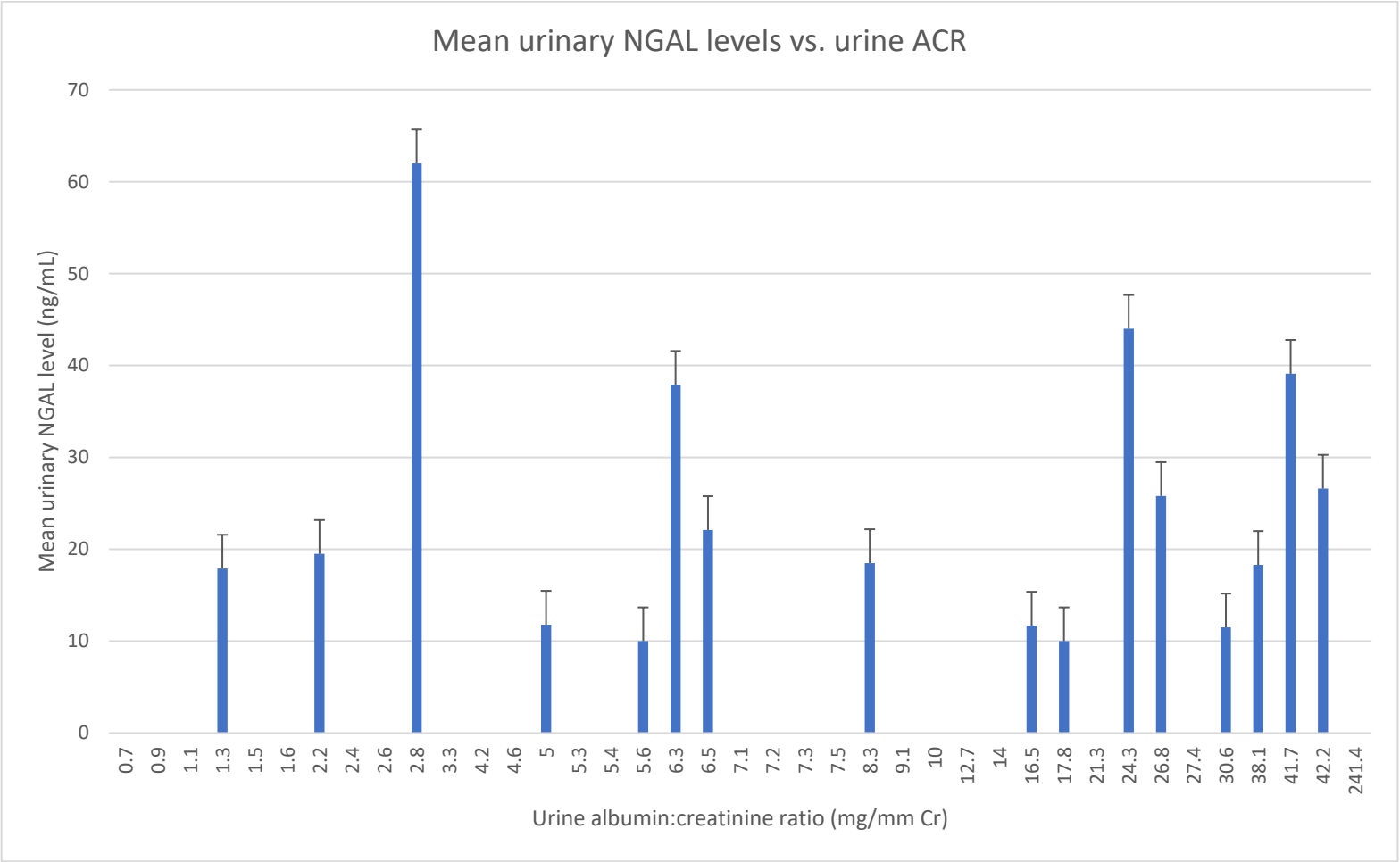
Figure 28. Urinary NGAL levels vs. date (for patient 18)



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

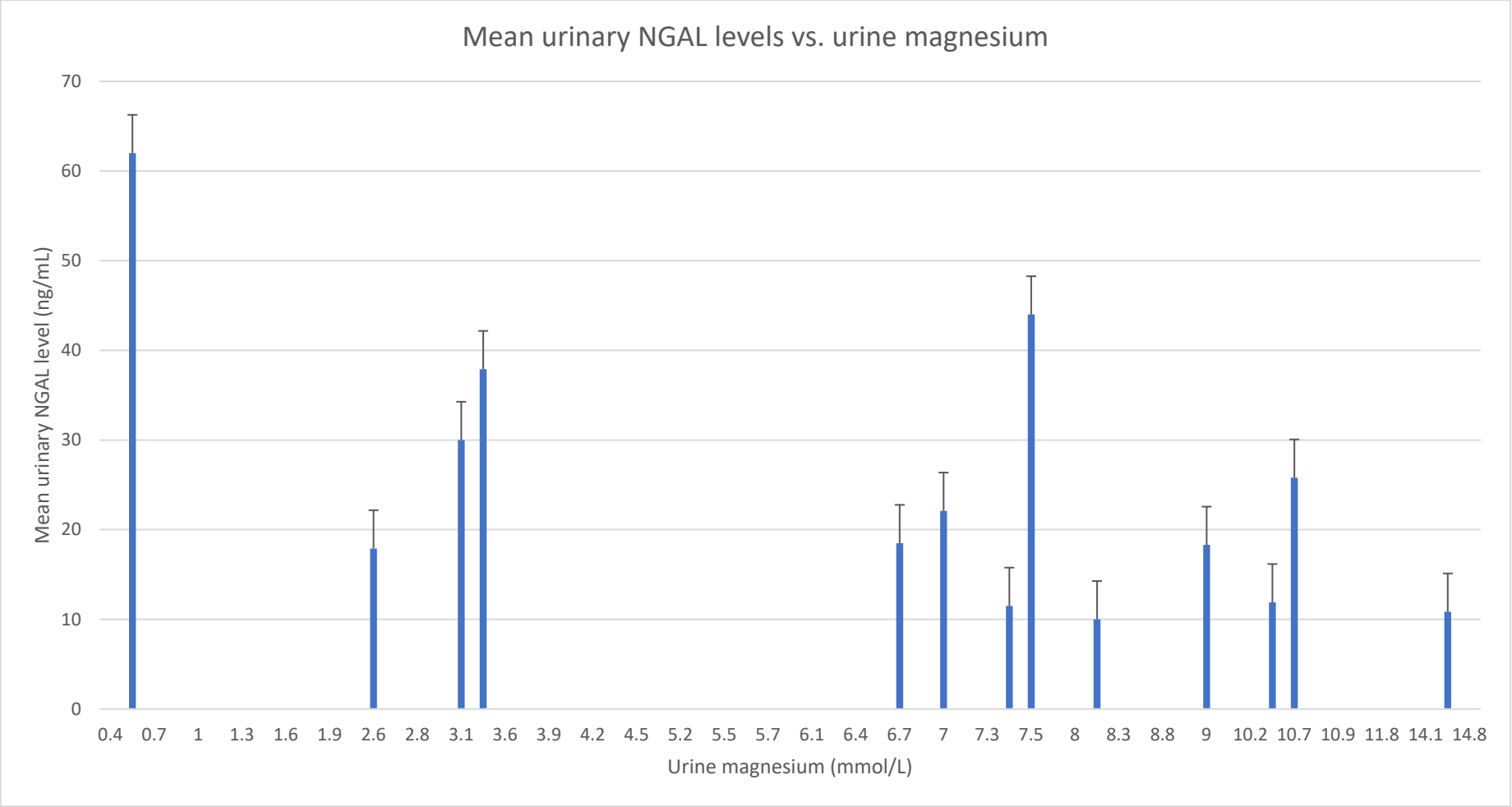
6.6. Appendix 6

Figure 29. Mean urinary NGAL levels vs. urine albumin: creatinine ratio (ACR)



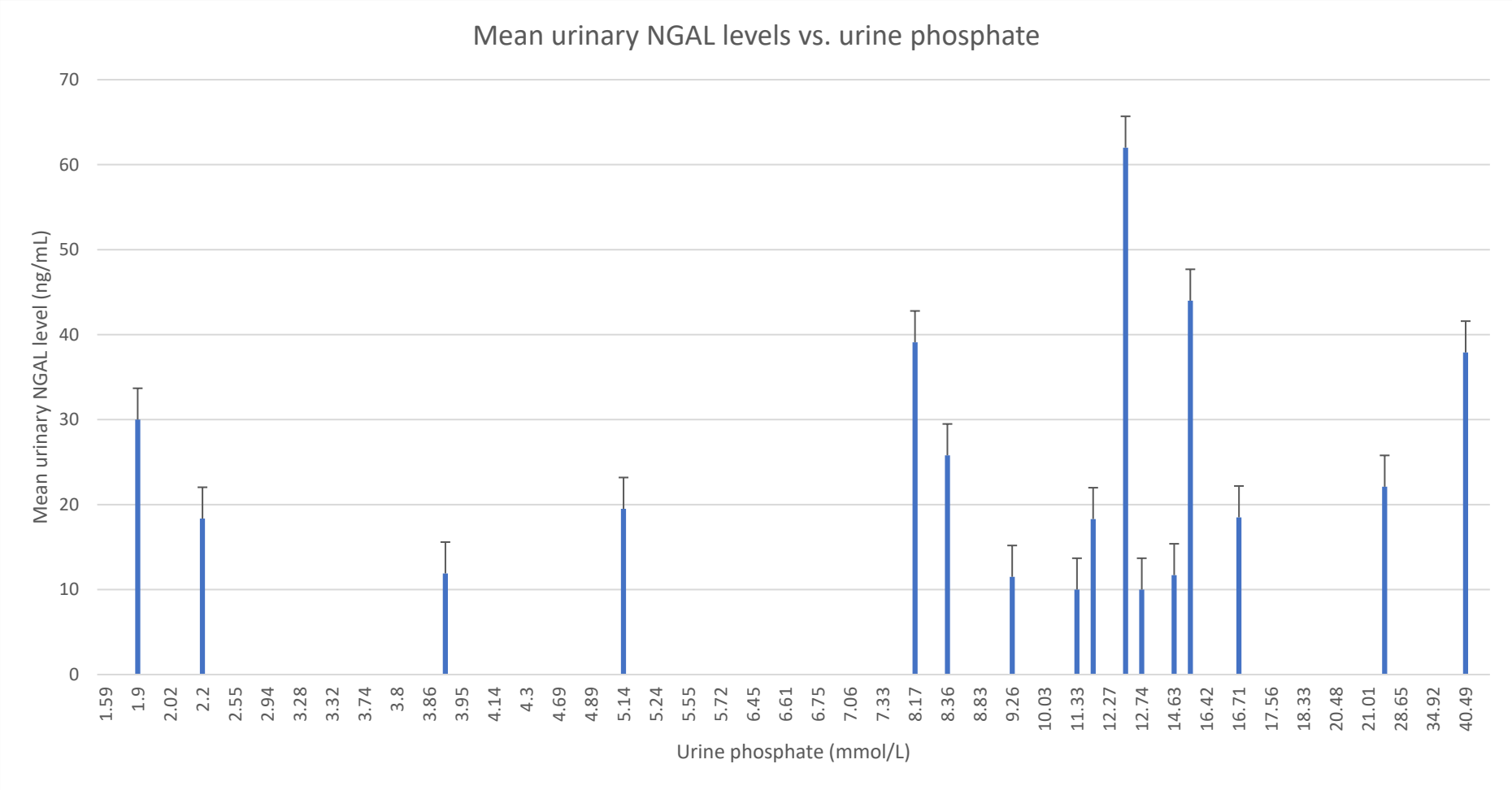
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 30. Mean urinary NGAL levels vs. urine magnesium



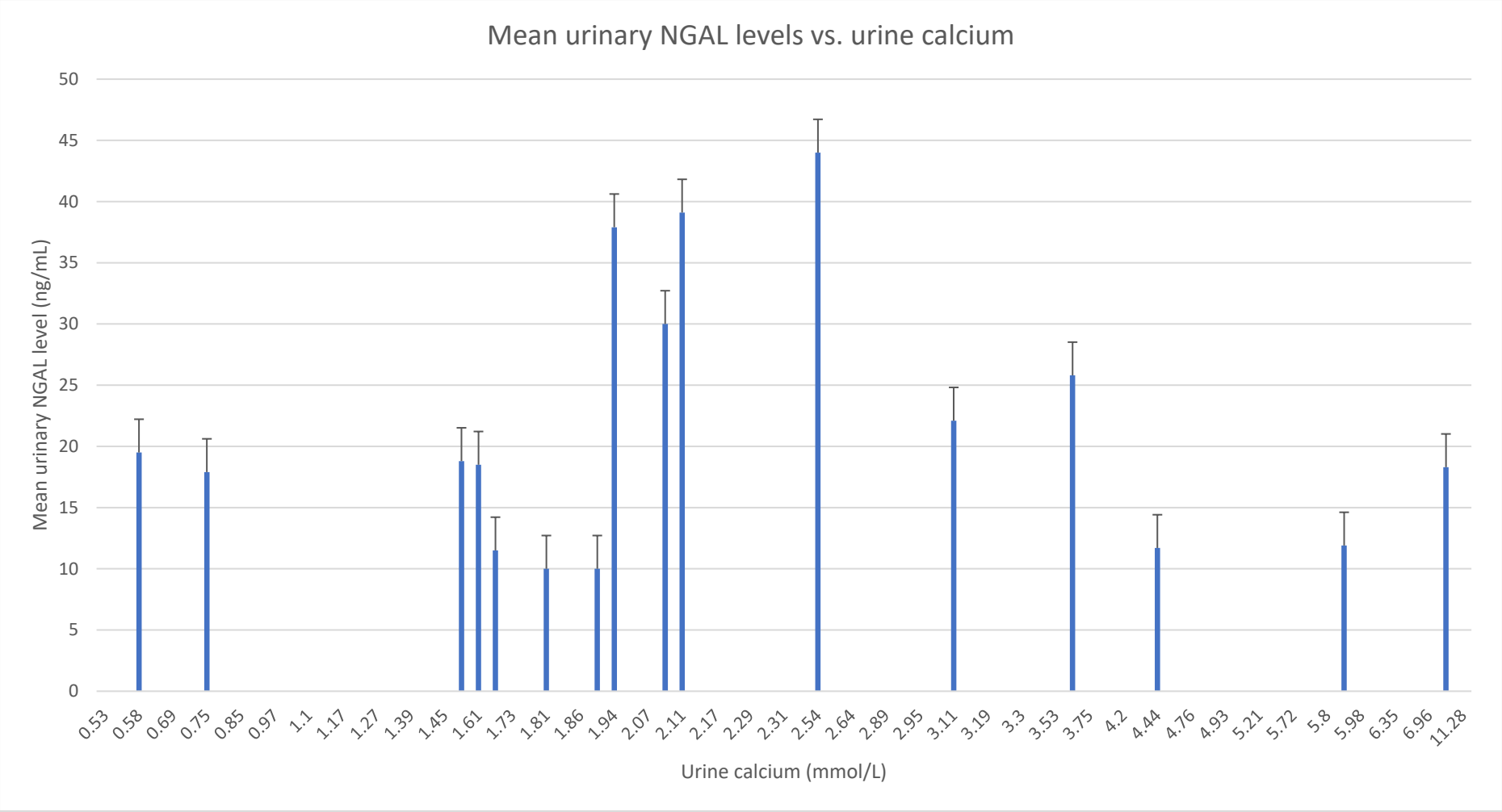
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 31. Mean urinary NGAL levels vs. urine phosphate



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

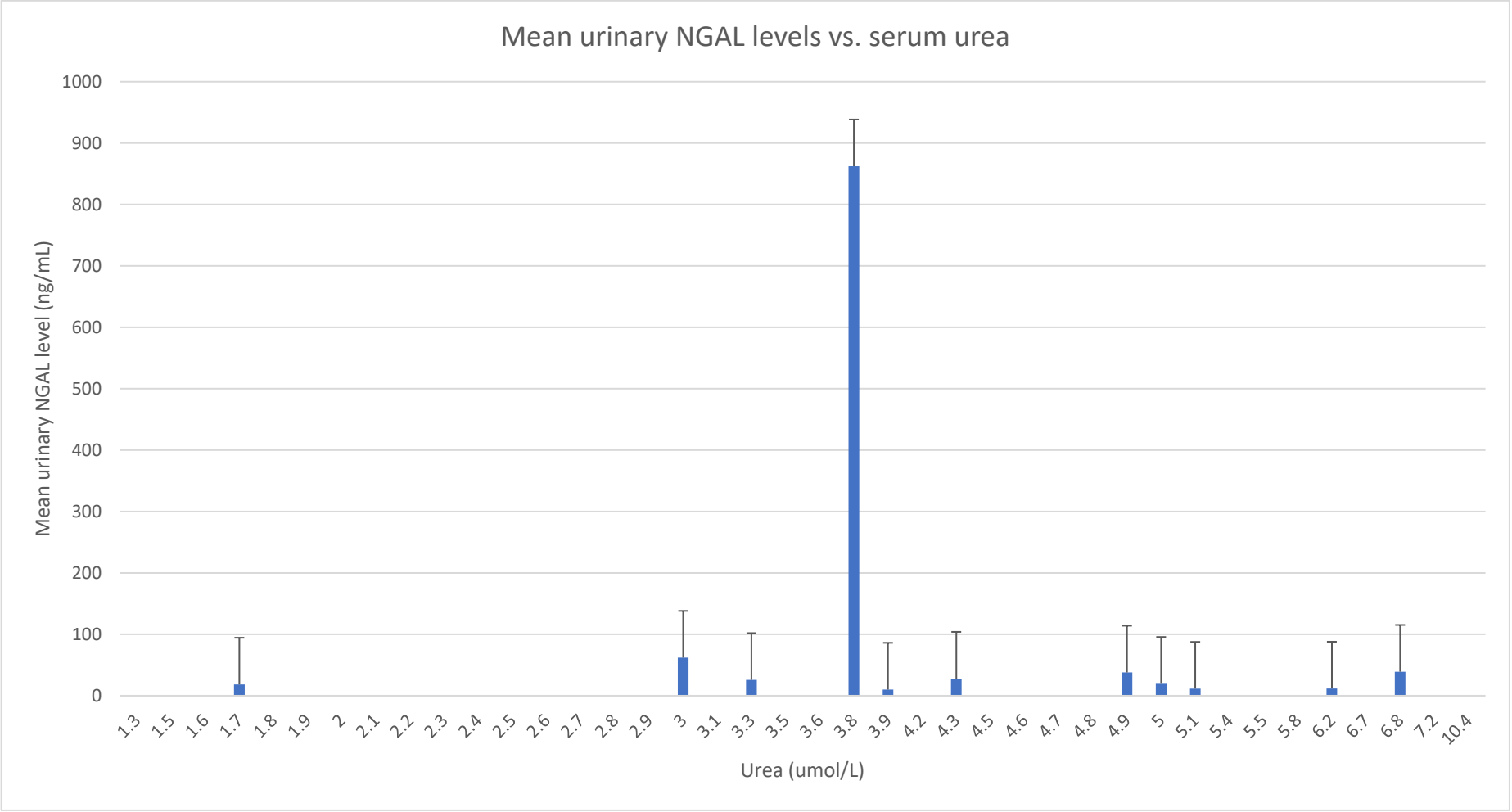
Figure 32. Mean urinary NGAL levels vs. urine calcium



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

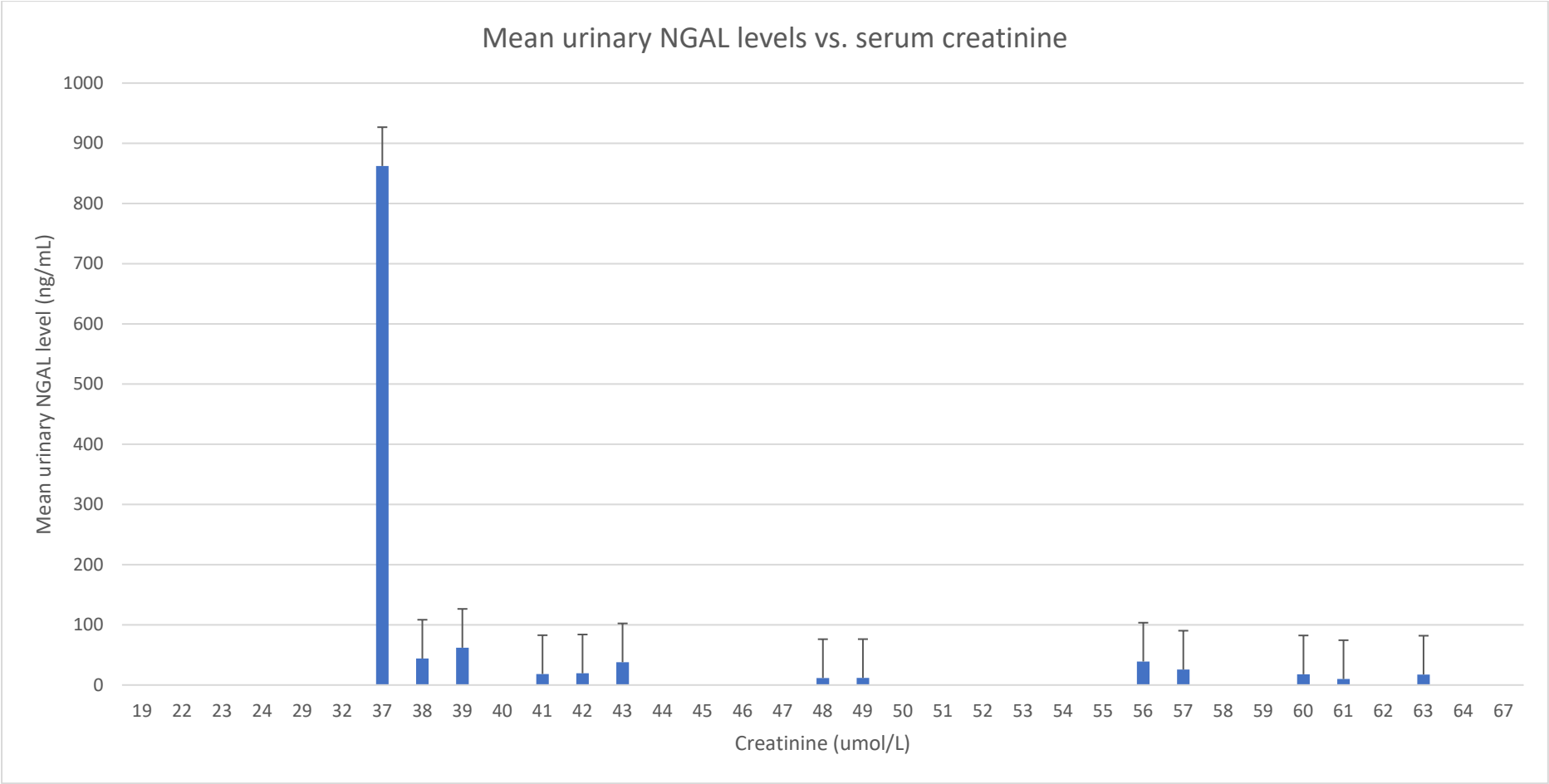
6.7. Appendix 7

Figure 33. Mean urinary NGAL levels vs. serum urea



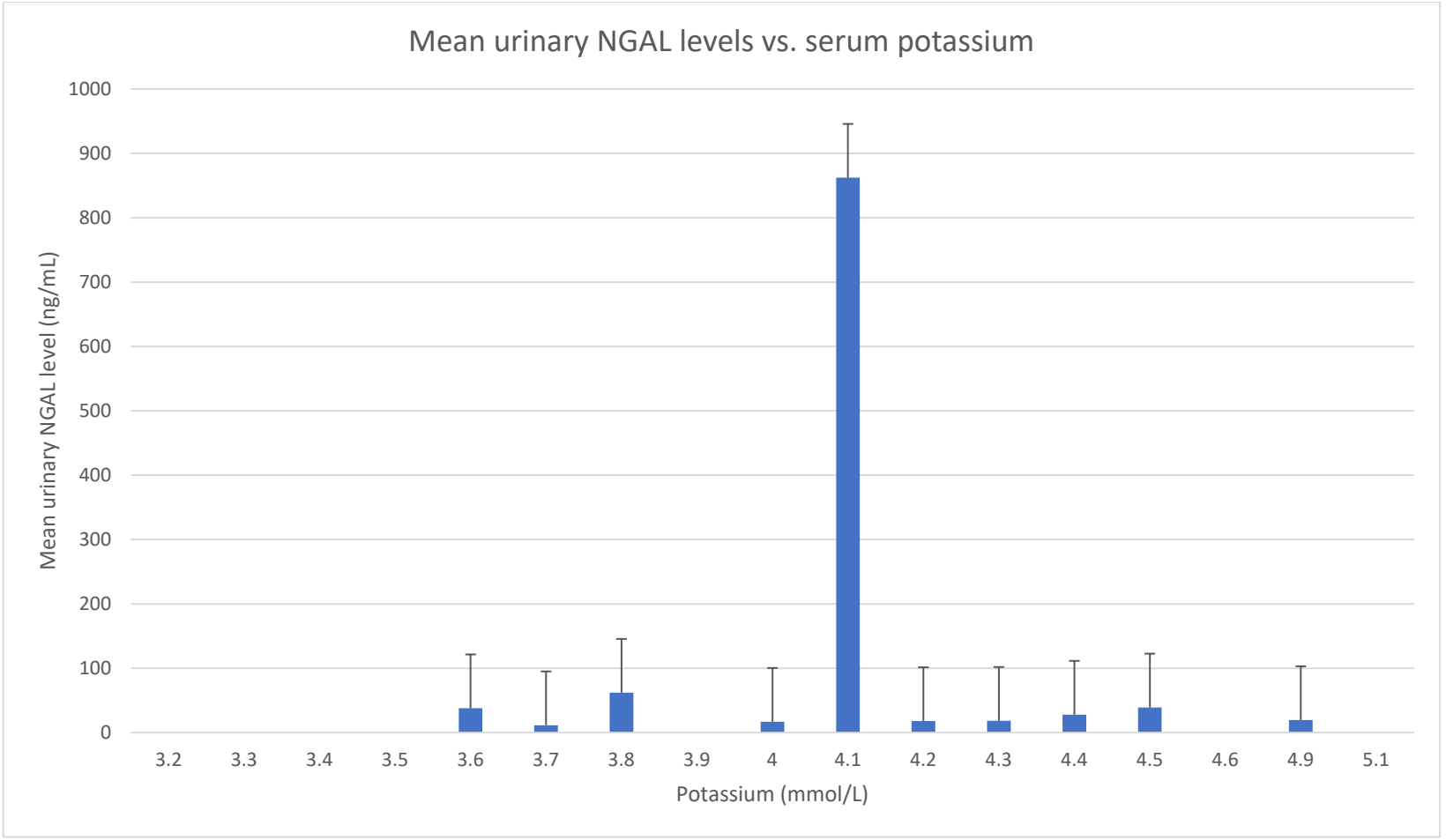
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 34. Mean urinary NGAL levels vs. serum creatinine



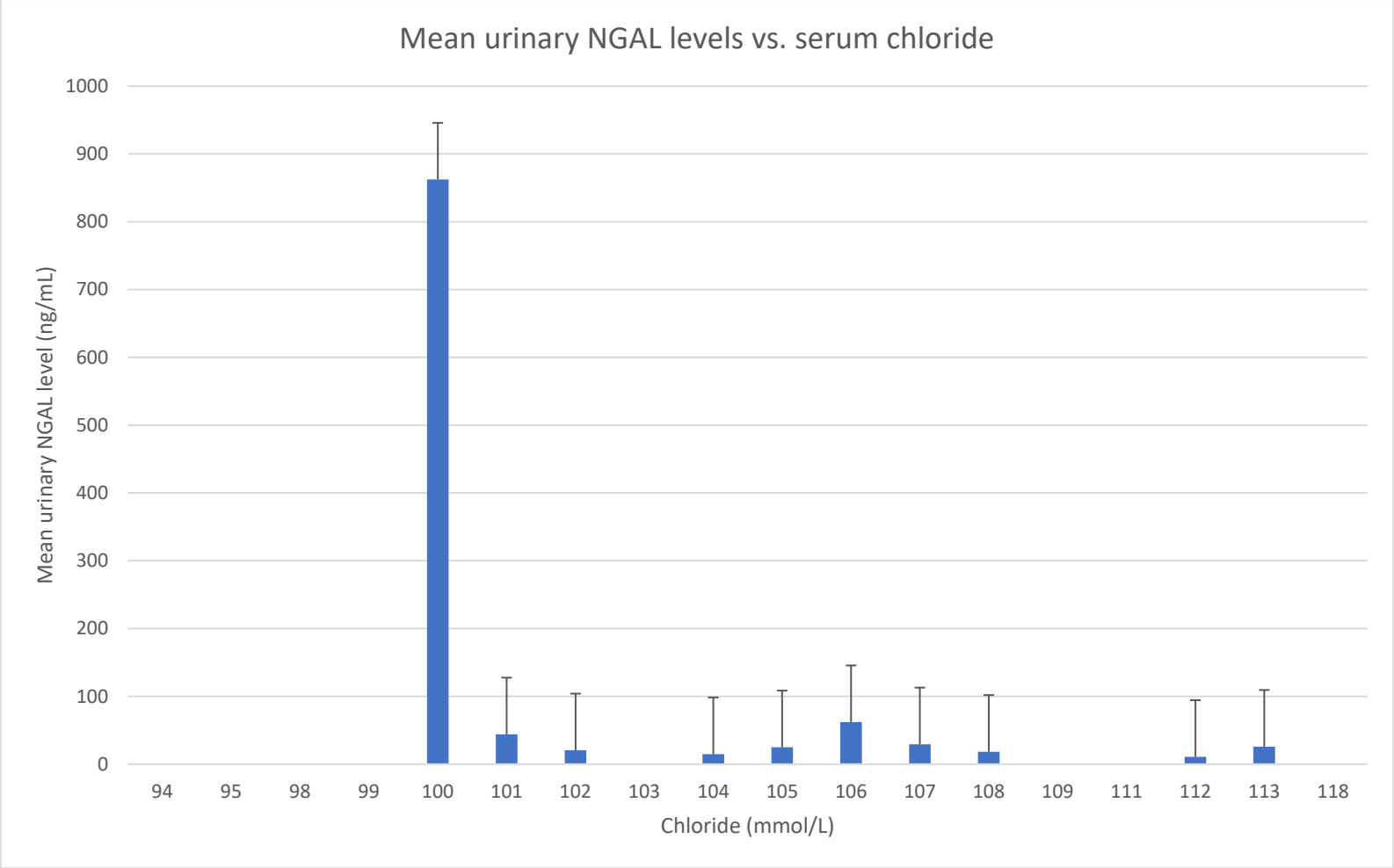
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 35. Mean urinary NGAL levels vs. serum potassium



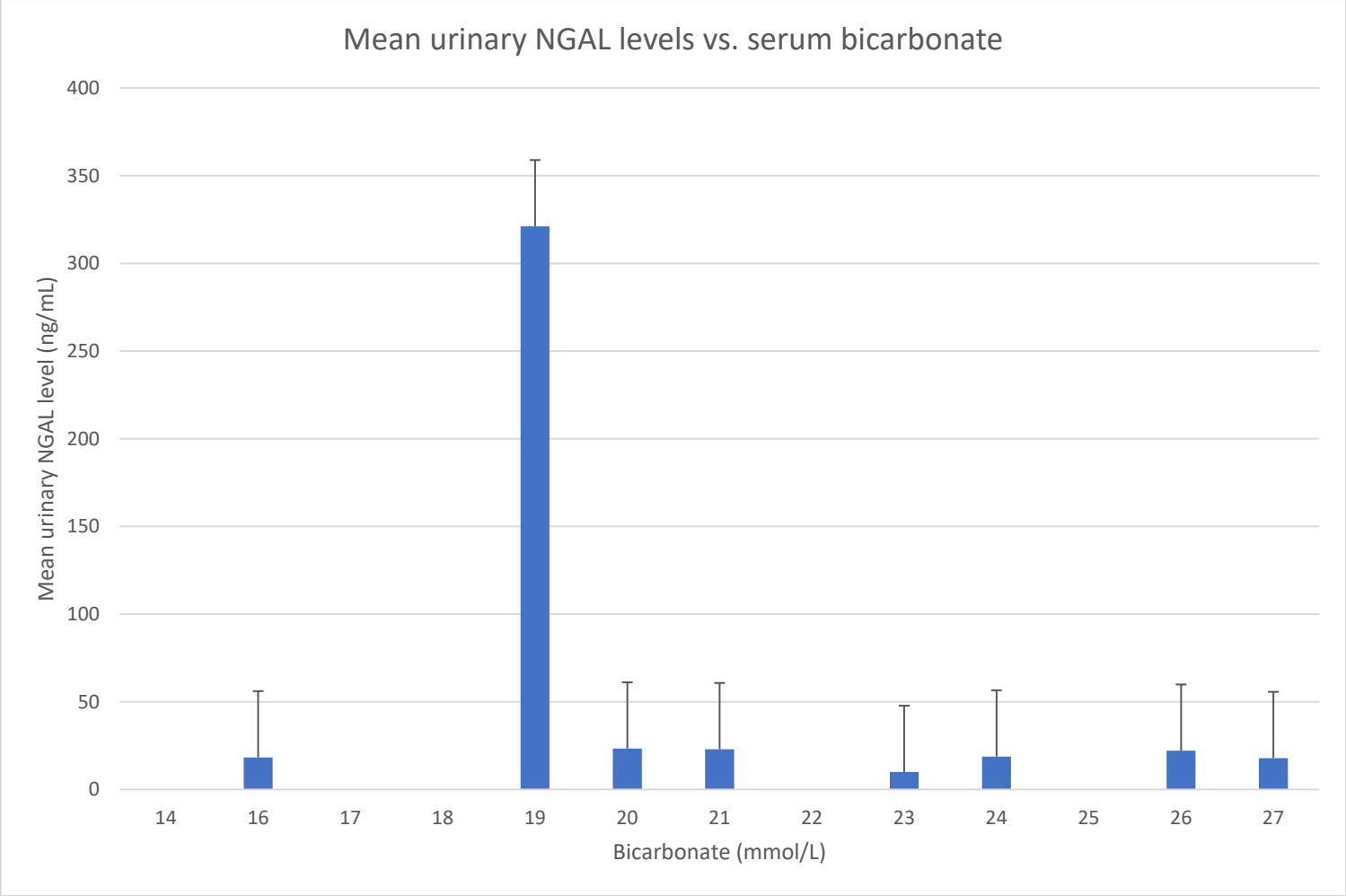
*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 36. Mean urinary NGAL levels vs. serum chloride



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).

Figure 37. Mean urinary NGAL levels vs. serum bicarbonate



*Missing bars denotes value lower than detectable levels of urinary NGAL (<10 ng/mL).