Distribution Agreement

In presenting this report as a partial fulfillment of the requirements for an advance degree from Emory University, I agree that the School of Public Health shall make it available for inspection and circulation in accordance with its regulations governing material of this type. I agree that permission to copy from, or to publish this report may be granted by the professor under whose direction it was written, or in his/her absence, by the Director of Career Education, when such copying or publication is solely for scholarly purposes and does not involve potential financial gain. It is understood that any copying from, or publication of this report, which involves potential financial gain will not be allowed without written permission.

Signature of Student Date

USING AREA UNDER THE CURVE AS A DECISION TOOL FOR CYTOMEGALOVIRUS VIRAL LOAD MANAGEMENT FOR KIDNEY TRANSPLANT PATIENTS

BY

Adriana C. Gibby
Degree to be awarded: M.P.H.
Executive M.P.H

Paula Braun, M.S., M.S.A., Committee Chair	Date
Aneesh Mehta, M.D., Field Advisor	Date
Jennifer Gander, M.S.P.H., Ph.D., Committee Member	Date
Laura Gaydos Ph.D. Associate Chair for Academic Affairs, Executive MPH Program	Date

USING AREA UNDER THE CURVE AS A DECISION TOOL FOR CYTOMEGALOVIRUS VIRAL LOAD MANAGEMENT FOR KIDNEY TRANSPLANT PATIENTS

BY

Adriana C. Gibby
M.P.H., Emory University, 2016
M.S., University of Minnesota, 2003
D.V.M., Universidad de Antioquia, 1993

Thesis Committee Chair: Paula Braun, M.S., M.S.A.

An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Executive MPH program
2016

Abstract

USING AREA UNDER THE CURVE AS A DECISION TOOL FOR CYTOMEGALOVIRUS VIRAL LOAD MANAGEMENT FOR KIDNEY TRANSPLANT PATIENTS

BY
Adriana C. Gibby

Chronic kidney disease (CKD) can lead to end-stage renal disease (ESRD), which is the form of CKD where life can be maintained only by dialysis or transplantation.[1] Transplantation has more benefits compared with chronic disease treatment. There is a significantly lower mortality associated with transplantation, and quality of life is better among transplant recipients.[2] However, the current organ shortage is a limiting factor and it is crucial to ensure and protect the graft from rejection.[3] Cytomegalovirus (CMV) is one of the most prevalent virus after transplantation that can cause significant morbidity, organ rejection, and adverse transplant outcomes.[4] Donor and Recipient CMV status are risk factors for CMV infection by primary infection or by reactivation.[5,6] Patients with Donor (+)/Recipient (– match have shown being at the higher risk to develop CMV.[7,8] To understand the CMV dynamics on kidney transplant patients, this study stratified risk groups based on CMV Donor/Recipient status (Donor (+)/Recipient (-): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk) and compared different immunosuppressive treatments and CMV viral load (amount of virus) in this population using area under the curve (AUC). AUC is the result of multiplying the individual CMV results and the different time points using a trapezoidal rule.[9] AUC analysis allows establishing the magnitude of the quantity of CMV. A data dictionary has been designed as part of the data capture tool using REDCap to support clinical operations monitoring transplant patients focusing on Cytomegalovirus high-risk. Our study found a significant association between CMV high risk (Donor positive/Recipient negative) having a higher AUC in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive). Results indicate no statistical significance among the different immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 related, to CMV measurements. The different immunosuppressive treatments might not be a risk factor for the occurrence of CMV. In summary, developing AUC and applying data capture, as an analytical tool will support clinical operations to monitor transplant patients focusing on the high-risk groups and having efficient resource allocation.

USING AREA UNDER THE CURVE AS A DECISION TOOL FOR CYTOMEGALOVIRUS VIRAL LOAD MANAGEMENT FOR KIDNEY TRANSPLANT PATIENTS

BY

Adriana C. Gibby
M.P.H., Emory University, 2016
M.S., University of Minnesota, 2003
D.V.M., University of Antioquia, 1993

Thesis Committee Chair: Paula Braun, M.S., M.S.A.

A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Executive MPH program
2016

ACKNOWLEDGEMENTS

I would like to dedicate my thesis to my husband John and my son Gabriel, who spent a lot of time together while I was completing this Master's degree. Thank you John for your words of encouragement and support when I was ready to give up.

I would like to thank and recognize my committee: Paula Braun (Chair), Aneesh Mehta (Advisor), and Jennifer Gander (Committee member) for their guidance and patience. Also, I cannot pass up this opportunity to recognize my instructors at the EMPH for their high quality teaching and knowledge.

Lastly, I would like to thank my coworkers and supervisors, Emory Transplant Center (ETC) personnel, and especially Rachel Patzer, for their support from the beginning.

Table of Contents

Chapter I: Introduction

Introduction and Rationale

Chronic kidney disease (CKD) is a progressive condition where the kidneys lose their function, which can lead to health detriment and in advance stages reduce life span.[1] There is enough evidence for CKD to considered a public health issue since: 1.) The disease burden is high. In the U.S., one in 10 American adults (more than 20 million people), have some level of CKD.[10] CKD incidence and prevalence are growing most rapidly in people ages 60 and older, and CKD has doubled between 2000 and 2008 in people ages 65 and older.[11] 2.) Although the overall prevalence of CKD in the U.S was low at 2.8% between 2001-2012, CKD has higher prevalence in specific regions.[12] CKD is distributed unevenly, disproportionately affecting minorities and specific ethnic groups: African Americans, American Indians, Alaska Natives, and Hispanics[13]; and 3.) There is evidence that upstream preventive strategies could reduce the burden of CKD. Each year assessing the care of patients at high risk for kidney disease is one of the goals of the Department of Health and Human Services and stated a primary goal of Healthy People 2020 was to "reduce new cases of chronic kidney disease and its complications, disability, death, and economic cost."[14]

CKD can lead to end-stage renal disease (ESRD), which is the form of CKD where life can be maintained only by dialysis or transplantation.[15] At this stage the kidneys fail to filter waste products. Transplantation has more benefits compared with chronic dialysis treatment. Compared to dialysis, there is a significantly lower mortality associated with transplantation, and quality of life is better among transplant recipients.[2] However, the current organ shortage is a limiting factor and it is crucial to protect the graft from rejection. Having viral infections like Cytomegalovirus increases the risk of graft failure. The most favorable scenario for graft survival has been associated with CMV seronegativity in both donor and recipient (D-/R-), and the most adverse graft survival has been associated with seropositive donors (D+/R-).[16] Until now, a complete analysis that allows establishing the magnitude of the quantity of CMV has not been done. We aim to accomplish this analysis using a method called area under the curve (AUC). The area under the curve is the result of multiplying the individual CMV results and the different time points using a trapezoidal rule.

AUC as a novel approach to understand viral dynamics in kidney transplant patient integrates clinical decision-support study that integrates analytical tools and end-user practitioners' requirements, which until now has not been done. Our research study aims to develop a capture tool to integrate standardized patient data that includes AUC. The capture tool will be an essential source for analysis to: (1) provide insightful information to the practitioners about CMV onset among immunosuppressive treatment cohorts developed at Emory Healthcare to improve transplant outcomes, (2) select the best treatment that contributes to public health solutions, and (3) improve resource allocation focusing on high-risk patients.

Problem Statement

To improve public health in relation to kidney disease, it is vital to have decision-making tools to identify high-risk groups and make prompt and effective decisions to avoid kidney (graft) rejection. Available kidneys, physician time and hospital space are scarce resources that need to be allocated carefully to maximize public health. The first three months after transplantation are decisive for every patient, since viruses like CMV can lead to rejection because the patients are under immunosuppressive treatments. Establishing the magnitude of the quantity of CMV will support clinical strategies and improve resource allocation. For example, identifying high CMV viral loads on specific groups of patients may lead to monitoring (testing) these every 15 days instead of once a month. Knowing this trend, more resources will be utilized on those patients that are more at risk, and/or scarce resources may be allocated to those with less risk. AUC will provide insightful information about CMV onset among immunosuppressive treatment cohorts that has never before been available to practitioners. The findings will allow making predictions about the resistance of CMV, the outcome, and CMV dynamics. Results may guide practitioners to make better decisions for the patients considering the CMV recipient/donor status and the immunosuppressive treatments available. The application of AUC as an analytical tool will contribute to public health solutions, ensuring the best possible transplantation outcomes, and improving resource allocation.

Specific Aims

Design a data capture tool using REDCap to support clinical operations monitoring transplant patients, focused on Cytomegalovirus high-risk groups to improve health care and ensure efficient resource allocation.

Assess the area under the curve (AUC) for Cytomegalovirus (CMV) as an analytical tool to contribute significantly to make prompt and effective clinical decisions that will impact public health solutions and transplant outcomes.

Purpose Statement

To understand the CMV dynamics on kidney transplant patients, we studied different immunosuppressive treatments and compare CMV viral load (amount of virus) in patients receiving a kidney transplant from April 2010 to January 2015. The measure of CMV was done using qPCR (Quantitative Polymerase Chain Reaction). Until now a complete analysis that allows establishing the magnitude of the quantity of CMV has not been done. The purpose of this study was to explore the use of the area under the curve (AUC) method for Cytomegalovirus (CMV) as an analytical tool to contribute significantly to make prompt and effective clinical decisions.

Definitions of Acronyms

AUC: Area under the Curve

qPCR: Quantitative Polymerase Chain Reaction is a technique used in molecular biology to amplify copies of DNA

LIMS: Library and IT Services

REDCap: research electronic data capture

Chapter II: Literature Review

Introduction

The following literature review will provide necessary context to the aims and objectives of the study. First, the review will discuss the nature of CMV and its relevance in transplantation. Second, it will offer a review of the strategies and treatment options to overcome CMV infection and explore the existing diagnostic tests and interpretations. Third, the review will elucidate the knowledge gap in the research and explain why we must explore new methods to understand CMV dynamics when different immunosuppressive therapies are in place. Last, the review will present a data capture tool using REDCap to support clinical operations to monitor transplant patients focusing on Cytomegalovirus.

CMV Occurrence and Impact in Transplantation

Cytomegalovirus (CMV) is a pathogen that affects transplanted patients causing high morbidity and potential high mortality.[17] CMV incidence among renal transplant patient can be between 8% and 32%.[5] The incidence of CMV for the renal transplant patients at Emory Healthcare is estimated to be 27%.[18] Establishing the viral load can support the prognosis, therapy, and antiviral treatment efficacy evaluation. Treatment efficacy evaluation includes: treatment duration selection, and establishment of the viral resistance.[19] CMV infection is expressed differently among organ-transplanted patients. CMV infections post-transplant varies from 2 weeks to several months. [7] The infection can be asymptomatic and it can be correlated with low viral load, or it can be life threatening with the presence of high viral load.[17] The immunosuppressive therapy might have an affect on the viral reactivation. Among kidney transplant patients, CMV infection can occur as an acute infection or as a viral reactivation. Without prophylaxis, acute infection can occur between the first and third months after transplant, which coincides with high levels of the patient's immunosuppression. New approaches in managing viral infections that

are using antiviral as a prophylaxis have delayed the CMV viral onset up to one year after transplant once the therapy has ended.[20]

Strategies and Treatment Options

Tacrolimus is an immunosuppressive used to reduce the patient's immune system response and lower the probability of organ rejection.[21] Tacrolimus activity is similar to cyclosporine. Emory Transplant Center at Emory University played a significant role to develop Belatacept[22], which was FDA approved in 2011.[23] Belatacept is a fusion protein capable of blocking the process of T-cell activation,[24] which aims to provide extended graft survival with less levels of toxicity in comparison to other immunosuppressive treatments.[25] The BENEFIT study, a randomized trial, has shown Belatacept to be an efficient and safe immunosuppressive used for a 5-year period on kidney transplant patients.[26] In addition, Belatacept-based immunosuppressive treatment has been associated with better allograft function, higher number of patients who have survived with a functioning graft, and enhanced cardiovascular/metabolic risk profile compared with a Cyclosporine A-based treatment.[27]

Ganciclovir was the first treatment approved to treat CMV infections. Intravenous (IV) ganciclovir is the first election for CMV treatment, since the oral formulation has limited bioavailability. Valganciclovir is quickly metabolized to active ganciclovir in the intestinal wall and liver. It has been replacing the oral ganciclovir for general prophylaxis and preemptive therapy for CMV. [28] Additionally, Glucocorticoids belong to the first group of medications that have been used to avoid rejection on transplanted patients.[29] Methylprednisolone and prednisone are used on different protocols in transplantation. Glucocorticoids target the T-cells, decreasing cytokine production and lymphocytic proliferation, and modify cellular trafficking in order to preserve the graft.[30]

Diagnosis

Laboratory testing for CMV is achieved using viral load through PCR and expressed on copies/mL. Establishing viral load supports decisions about when to begin preemptive therapy, diagnose disease, and monitor response to therapy. Molecular assays based on real-time amplification and detection provides broad linear range, low limits of detection and quantification, and offer lower risk of contamination. However, some limitations are related with the interpretation and application to clinical care. The clinical value of low levels of CMV DNA (<100-500 copies/mL) has been difficult to interpret. Some studies have shown that the relevance of both the viral load value and the rate of change in viral load are important predictors of the development of the disease.[31]

Diagnostic Methods for CMV

Serological tests are used to detect CMV IgG, which will determine whether a patient had a CMV infection in the past. Complement fixation, enzyme-linked immunosorbent assay (ELISA), anticomplement immunofluorescence, radioimmunoassay, and indirect hemagglutination are some of the different techniques to detect CMV IgG antibodies. CMV IgM antibodies have been used to describe acute or recent infection. However, it is cumbersome to differentiate primary infections from viral reactivation, since the IgM can be present for months after the primary infection.[16,32]

Risk factors

Several factors such as the sero status of the donor and recipient, the type of organ transplanted, the immunosuppressive state, and viral factor are involved in the risk of developing CMV. Also, opportunistic infectious have been associated with risk factors, including younger age and CMV donor (+)/recipient (-), and these patients have presented a higher incidence of rejection.[33]

Epidemiology

It has been reported that transplant kidney patients who received valganciclovir prophylaxis were diagnosed with CMV within a year of transplantation. The group of patients where the donor and the recipient were positive (D+/R+) presented a higher rate of the disease (22%). Additionally, the group of patients D+/R- showed with late-onset CMV disease (19.2%).[34] Extending CMV prophylaxis up to 200 days with valganciclovir has reduced the incidence of late-onset CMV disease in the D+/R- group. [35] CMV remains latent in different cells and present intermittent episodes during the reactivation. [36] There are different classifications based on the donor-recipient status. High-risk patients represent those without immunity against CMV (R-), who receive an organ from CMV seropositive donor. [37]

Area Under the Curve – Exploring New Methods

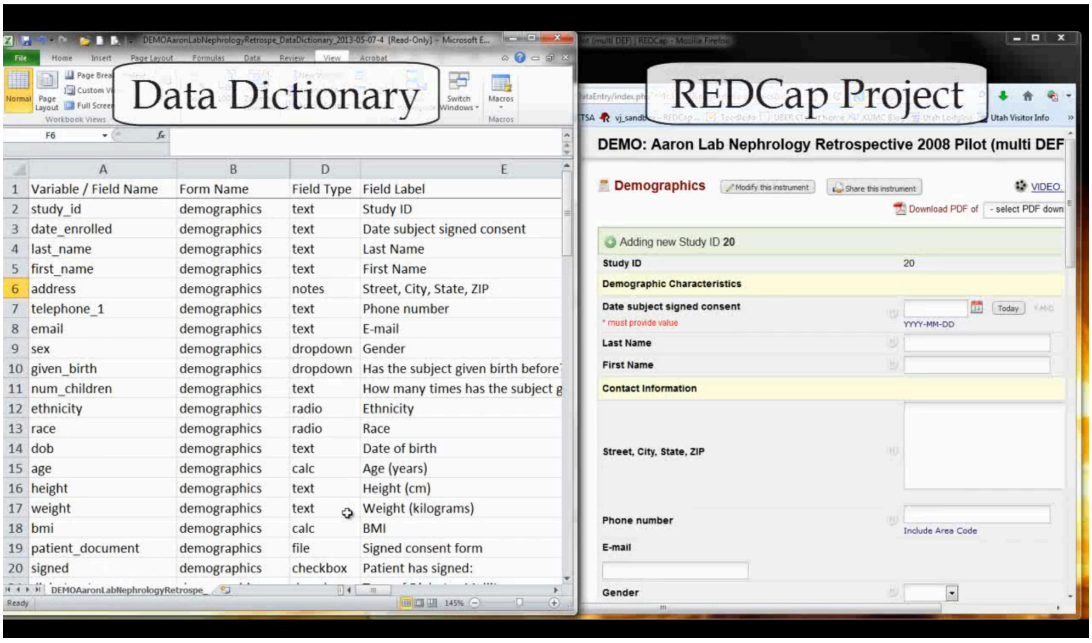
Area under the curve has been described as a novel approach to analyze viraemia, which is defined by its level and its duration. [9] AUC has demonstrated to be an innovated and accurate technique to detect patients who are at risk to develop symptomatic CMV infection.[9]

REDCap – A Data Capture Tool

Research Electronic Data Capture (REDCap) is an adaptable and valuable browser-based, metadata-driven (software solution), and working methodology for designing clinical and translational research databases.[38] The data dictionary supports the data that is collected for different data collecting periods. Figure 1 depicts the data dictionary and REDCap tools hosted at Emory University.[39] The data dictionary is created on Excel spreadsheets, which contain columns, fields, and variables. Columns are functional according to the study.[38,39] See Appendix A.

1. Column A: Variable/Field Name, Variable names.
2. Column B: Form Name
3. Column C: Section Header
4. Column D: Field Type
5. Column E: Field Label
6. Column F: Choices, Calculations, or sliders labels
7. Column G: Field Note
8. Column H: Text Validation Type
9. Columns I & J: Text validation
10. Column K: Identifiers
11. Column L: Branching Logic

Figure 1. Data Dictionary supporting the data collected



	A	B	D	E
1	Variable / Field Name	Form Name	Field Type	Field Label
2	study_id	demographics	text	Study ID
3	date_enrolled	demographics	text	Date subject signed consent
4	last_name	demographics	text	Last Name
5	first_name	demographics	text	First Name
6	address	demographics	notes	Street, City, State, ZIP
7	telephone_1	demographics	text	Phone number
8	email	demographics	text	E-mail
9	sex	demographics	dropdown	Gender
10	given_birth	demographics	dropdown	Has the subject given birth before
11	num_children	demographics	text	How many times has the subject g
12	ethnicity	demographics	radio	Ethnicity
13	race	demographics	radio	Race
14	dob	demographics	text	Date of birth
15	age	demographics	calc	Age (years)
16	height	demographics	text	Height (cm)
17	weight	demographics	text	Weight (kilograms)
18	bmi	demographics	calc	BMI
19	patient_document	demographics	file	Signed consent form
20	signed	demographics	checkbox	Patient has signed:

Chapter III: Methodology

Introduction

"Using Area Under the Curve as a Decision Tool for Cytomegalovirus Viral Load Management for Kidney Transplant Patients" was conducted at Emory Healthcare and included kidney transplant patients. To evaluate the research questions, the data was collected from April 2010 to January 2016. The area under the curve (AUC) for Cytomegalovirus (CMV) was assessed for each patient. Groups were stratified based on CMV Donor/Recipient status (Donor (+)/Recipient (-): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk). A Mann-Whitney U test was performed to establish the differences among stratified groups and AUC. In addition, Mann-Whitney U test was performed to establish the differences among CMV viral loads from the AUC among the immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5. Also, using REDCap, a data dictionary was developed to support clinical operations to monitor transplant patients focusing on Cytomegalovirus high-risk groups to improve health care and ensure efficient resource allocation.

Population and Sample

The sample population included Emory Healthcare's kidney transplant recipients from April 2010 to January 2015. Patients were included if they had: 1.) At least 2 positive CMV results after any time post transplantation and 2.) ≥365 days of clinical post-transplantation. To obtain ≥365 days of follow-up post-transplant, data was collected on patients through January 31, 2016. Thus, patients who were transplanted on or before January 31, 2015 were included in order to have a representative number of tests among the different immunosuppressive treatments.

During July 1, 2012 and December 31, 2014, Emory Healthcare's surgeons performed 940 adult kidney transplants.[40] Considering that 27% Emory patients have been positive to CMV,[18] it was estimated to have a sample that included 233 patients. See formula below.

Sample size = Approximate number of patients transplanted from 2010 to 2015 x % CMV positive patients at Emory.

Sample size = 862 x 27% = 233

However, the sample size for this study included 119 patients that complied with the inclusion criteria described above. The dataset included patients with the following identifiers: names, medical record number, and dates. Therefore, the data was de-identified through moving, recoding identifiers, and replacing explicit references to dates.

Research Design

The following protocol was performed at Emory Healthcare, Atlanta, GA. All kidney transplant candidates were screened for CMV antibodies using Immunoglobulin G (IgG) at time of transplant evaluation. CMV-positive patients went under prophylactic treatment using Valganciclovir Hcl (Valcyte). The treatment duration was based on donor/recipient status for CMV. Donor (+)/Recipient (+) and Donor (-)/Recipient (+) for three months, Donor (+)/Recipient (-) for six months, which has been considered as high risk. Donor (-)/Recipient (-) did not receive prophylaxis[18]. Table 1 illustrates Donor and Recipient CMV status at time of kidney transplant and CMV risk category.

Table 1. Donor and Recipient CMV status at time of kidney transplant and CMV Risk Category

	Recipient CMV positive	**Recipient CMV negative**
Donor CMV positive	+/+ Moderate High Risk	+/- High Risk
Donor CMV negative	-/+ Moderate Low Risk	-/- Low Risk

PCR testing was performed one month after the transplant date, and then monthly for the first year and continued based on the patients' symptomatology. Our study stratified groups based on AUC and the risk groups based on CMV Donor/Recipient status. See Table 1 above. Emory's immunosuppression regiment had undergone transformations since April 2010 and the data included the following cohorts based on the immunosuppressive treatment: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5. The date ranges for the initial protocol start dates associated with the various Belatacept and Tacrolimus 1.5 treatment groups[41] are as follows:

Belatacept 1.0/1.1: July 26, 2011 - December 14, 2011 and
December 8, 2011 - June 12, 2012
Belatacept 2.0: May 6, 2012 - November 29, 2012
Belatacept 2.2: August 28, 2012 - October 25, 2013
Belatacept 2.3: November 1, 2013 - March 14, 2016
Tacrolimus 1.5: April 21, 2010 - July 11, 2016

Since there is some overlap among the starting dates within the treatment groups, the dataset included the information about the treatment group with which the patient was associated at the time of transplant.

An expedited approval IRB 00086886 was obtained from the Institutional Review Board at Emory University on 2/29/2016 and the approval for the

amendment was obtained on 06/10/2016. The approval included both, a waiver of informed consent and a complete HIPAA waiver for the conduct of this study.

Procedures

Procedures for Medical Record Review

Since this was a retrospective chart review, Emory Healthcare had already collected the data for this study and it was included in the patient's medical chart. The data was obtained from an Informatics Analyst from the LITS (Library and IT Services): IT Data Management & Solutions department at Emory University with access to the Emory Healthcare database. The Informatics Analyst queried the PHI that was required for this study, which included: Patient name, Emory University Hospital medical record number, Transplant Date, CMV test date, CMV result, date of graft failure, and Date of death; and additional information such as Treatment cohort

Instruments

In order to ensure the security of protected health information I complied with the administrative, physical, and technical safeguards that Emory Healthcare and Emory University had in place. Patient health information concerning to this study was de-identified as is defined in the HIPAA Privacy Rule, Code of Federal Regulations, 45CFR164.514, as "Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual is not individually identifiable health information"[42]. Since our dataset had the following identifiers: names, medical record number, and dates, the data was de-identified through moving, recoding identifiers, and replacing explicit references to dates. The patient's name was removed. The original Medical Record Number was modified ('re-coded'), and the dates were replaced.

Patient Name

The dataset was provided in Excel format containing patient names. Using the deleting tool, the patient name column was removed.

The Medical Record Number

The Medical Record Number was re-coded using a new randomly identifier to each participant. The dataset included the new random participant identifier that was sorted using a new identifier to ensure the original order was changed. SAS (9.4 version) software was used to create a unique 6 digit random number using a code called: "%DEIDNUM", which generated a variable called "deidnum" for the new unique 4 digit random number[43].

Dates related to the patient information health

The original dataset included the following dates related to the patient:
Transplant Date
CMV test Date
Date of graft failure

Date of Death

We de-identify the following dates: Transplant Date, CMV test date, date of graft failure, and Date of death, using the "Offset Date" method[43]. Using this method all dates were replaced with a new date generated using a random offset for each participant. The offset method was applied to all dates in the study for each patient, which maintained the relative distance among the participant's dates and among different participants. SAS (version 9.4) software was used to target the original dates and convert them to floating point number offsets. SAS (version 9.4) will generate a new variable called "Studyday of" and incorporate the key name of the original dataset e.g., the new name for "Transplant Date" will be "Studyday of Transplant Date." Anonymization as a following step to de-identification that involves destroying any links between the de-identified dataset and the original dataset was performed. To anonymize the data, the key code that was used to generate these new random identifiers was irreversibly destroyed.

Data Analysis

The data collection tool was developed based on the requirements collected from the research team and AUC parameters described below.

The dataset was validated and went through the process of data cleaning. Patients were included if they had: 1.) At least 2 positive CMV results after any time post transplantation and 2.) ≥365 days of clinical post-transplantation. SAS (version 9.4) software was used to perform statistical analysis.

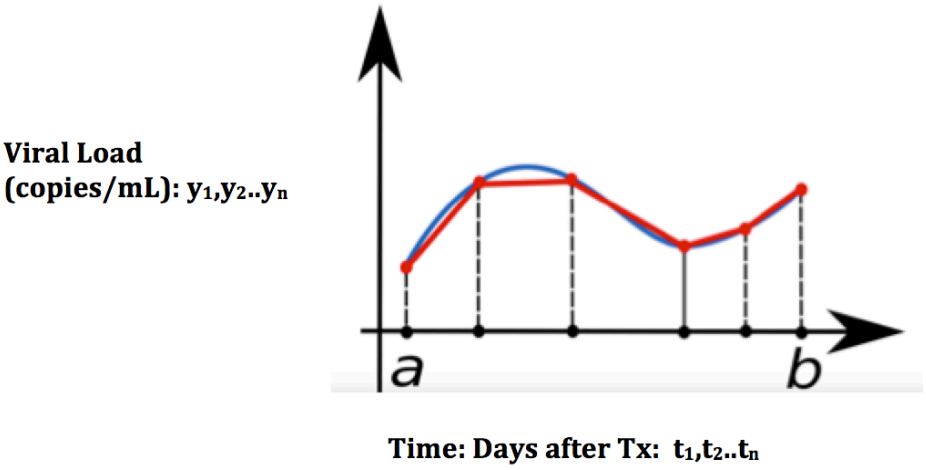
Area Under the Curve (AUC)

The area under the curve (AUC) for CMV PCR results was calculated for each patient by multiplying the total of trapezoid areas. AUC calculation involved each set point (days) from transplantation, which were expressed as $t_1,t_2,t_3...t_n$. and the corresponding measuring viral load (copies/mL), were represented as $y_1,y_2,y_3...y_n$. Figure 2 illustrates the AUC calculation using the trapezoid rule.[44]

Both variables, "days from transplantation" and the corresponding "viral load measurement" (copies/mL), were used to calculate the AUC using the equation below.[9] The AUC calculation is expressed in copies/mL*days or copies*day/mL.[45]

$$\mathrm{AUC_n} = \frac{1}{2}\sum_{i=1}^{n-1}(t_{i+1} - t_i)(y_{i+1} + y_i).$$

Figure 2. Area Under the Curve Calculation Using Trapezoid Rule



SAS (version 9.4) software was used to calculate the AUC using the following adapted code [46]:

```
data forArea;
set LongData;
by subjectID;
prevTime = lag(time);
prevMsr = lag(measure);
timeDiff =time - prevTime;
areaRect = timeDiff * (measure + prevMsr) / 2;
if first.subjectID
then do;
prevTime = . ;
prevMsr = . ;
timeDiff = . ;
areaRect = . ;
end;
run;
proc means data= forArea sum;
class subjectID;
var areaRect;
output out=summation sum=AUC;
run;
```

The results obtained from the code described above were validated using another method using SAS (version 9.4) to calculate AUC per individual patient to confirm the accuracy of the results, as follow[47]:

```
DATA Datafile;
LENGTH Xtime Yvalue 8;
```

```
INFILE DATALINES;
INPUT Xtime 5.1 Yvalue 6.2;
DATALINES;
0.0         4.53
0.5         8.40
1.0         8.40
2.0         5.40
;
RUN;
```

The area under the curve (AUC) for Cytomegalovirus (CMV) was assessed for each patient. Groups were stratified based on CMV Donor/Recipient status (Donor (+)/Recipient (-): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk). First, a Mann-Whitney U test was performed to establish the differences among stratified groups and AUC. Second, a Mann-Whitney U test was performed to establish the differences among CMV viral loads from the AUC among the immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5. Each treatment group was evaluated at 400 days, 600 days, and 1400 days post transplantation.

REDCap as Data collection tool

A data dictionary was developed as part of the workflow methodology and software of research electronic data capture (REDcap). The data dictionary can be used for clinical data from transplant patients to monitor CMV at Emory Healthcare and might be a source to develop a data collection tool (See Appendix A).

Chapter IV: Results

Area Under the Curve (AUC)

Overall, 119 patients were included in this study. There were 44,8,65, and 2 patients in the High, Moderate-Low, Moderate-High, and Low CMV Risk groups respectively. Table 2 illustrates CMV Risk Status.

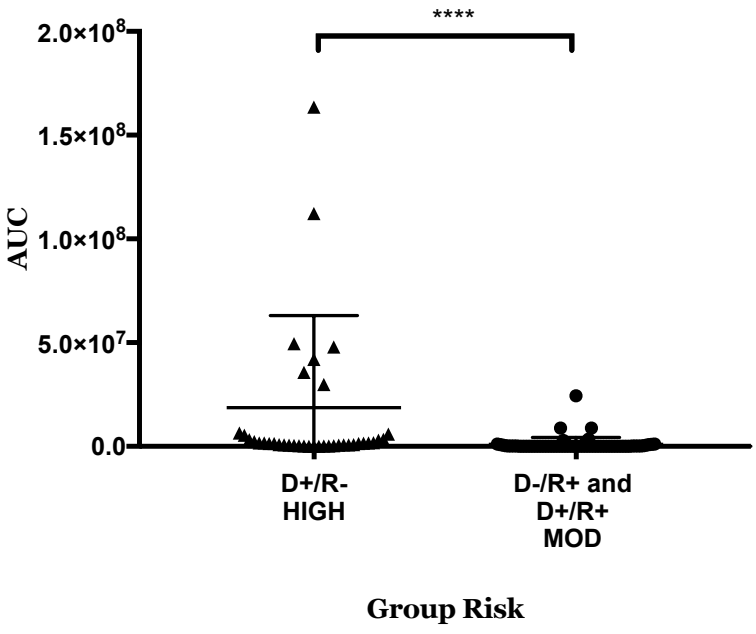
The area under the curve (AUC) for Cytomegalovirus (CMV) was assessed for each patient. Groups were stratified based on CMV Donor/Recipient status (Donor (+)/Recipient (-): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk). A Mann-Whitney U test was performed to establish the differences among stratified groups and AUC.

Table 2. CMV Risk Status

CMV Risk	Group	Donor	Recipient	Total	Tac 1.5	B 1.0/ 1.1	B 2.0	B 2.2	B 2.3
HIGH	1	P	N	44	14	8	5	8	9
MODERATE LOW	2	N	P	8	1	2	1	2	2
MODERATE HIGH	3	P	P	65	13	14	7	15	16
LOW	4	N	N	2	1	0	0	1	0
Total				119	29	24	13	26	27

We used the Mann-Whitney U test to compare CMV viral loads for CMV risk status according to the group. Our study found significant association between CMV high risk (Donor positive/Recipient negative) and higher magnitude and quantity in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive) at 400 days after transplantation ($p<0.0001$). Figure 3 presents AUC for High and Moderate Groups 400 days post-transplant.

Figure 3. AUC for High and Moderate Groups 400 days post-transplant

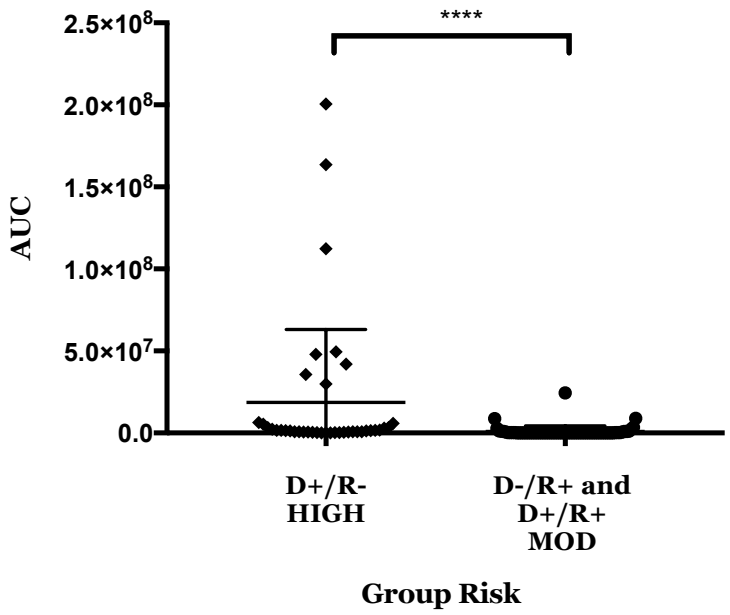


****. p=0.0001

The AUC medians for CMV risk group 400 days are as follow:
Median of High Risk Group (copies*day/mL) 1176748, n=39
Median of Moderate Risk Group (copies*day/mL) 52288, n=65

Also, using the Mann-Whitney U test to compare CMV viral loads for CMV risk status by risk-status group, this study found significant association between CMV high risk (Donor positive/Recipient negative) and higher magnitude and quantity in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive) at 600 days after transplantation ($p<0.0001$). Figure 4 illustrates AUC for High and Moderate Groups 600 days post-transplant.

Figure 4. AUC for High and Moderate Groups 600 days post-transplant



****. p=0.0001

The AUC medians for CMV risk group 600 days are as follow:
Median of High Risk Group (copies*day/mL) 1464151, n=39
Median of Moderate Risk Group (copies*day/mL) 71941, n=65

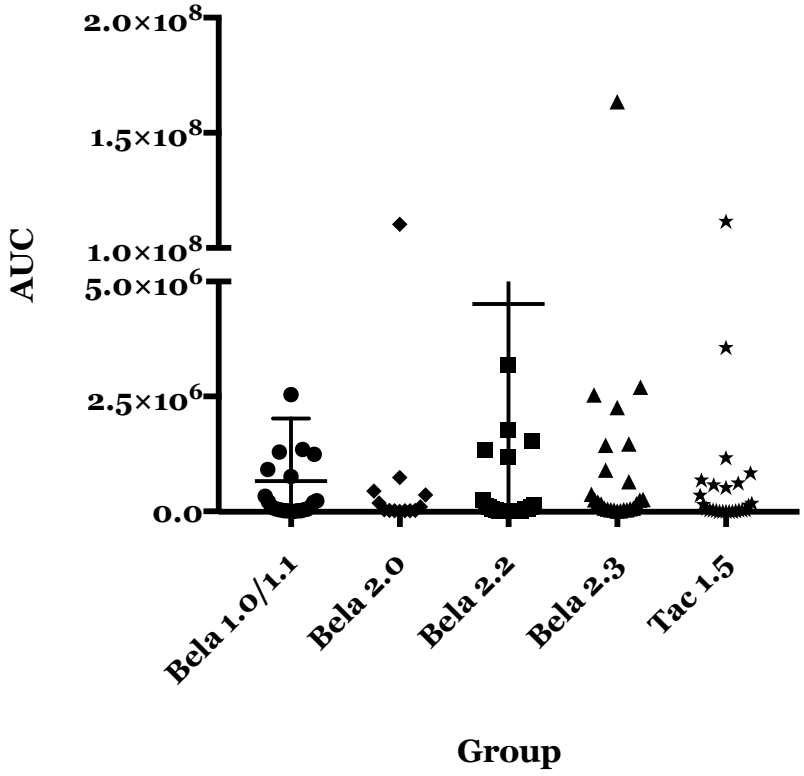
The plasma viral load was collected one month after the date of transplant for PCR testing, and then monthly for the first year and continued based on the patients' symptomatology. Emory's immunosuppression treatment included the following cohorts based on the immunosuppressive treatment: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5; see Table 3.

Table 3. Number of Kidney Transplant Recipients per Immunosuppression Treatment, April 2010-January 2015

Treatment	Number of Patients
Belatacept 1.0/1.1	24
Belatacept 2.0	13
Belatacept 2.2	26
Belatacept 2.3	27
Tacrolimus 1.5	29
Total	**119**

The area under the curve (AUC) for CMV PCR results was calculated for each patient by multiplying the total of trapezoid areas. Each treatment group was evaluated at 400 days, 600 days, and 1400 days post transplantation. AUC results by immunosuppression treatment group 400 days post-transplant are shown at Figure 5.

Figure 5. AUC by Immunosuppressive Treatment Group 400 days post-transplant



We used Mann-Whitney U test to compare CMV viral loads after calculating AUC among groups, our study did not find any significant difference among CMV viral loads from the AUC among groups; see Table 4.

Table 4.Comparison of AUC Belatacept groups vs. Tacrolimus 1.5

	400 days post-transplant		600 days post-transplant		1400 days post-transplant	
Group	**Median AUC**	**p-value***	**Median AUC**	**p-value***	**Median AUC**	**p-value***
Tacrolimus 1.5	145,209	--	521,076	--	521,076	--
Belatacept 1.0/1.1	98,948	0.7884	102,357	0.1921	314,747	0.8863
Belatacept 2.0	34,142	0.3983	97,536	0.1177	107,267	0.1612
Belatacept 2.2	101,117	0.6905	218,839	0.555	1420,369	0.102
Belatacept 2.3	248,608	0.3291	251,937	0.8762	251,937	0.7741
*p-value obtained through Mann-Whitney test comparing median AUC; reference group was Tacrolimus 1.5						

Data Dictionary

The following data dictionary was an adaptation as part of the workflow methodology and software of research electronic data capture (Redcap) to monitor CMV for transplant patients at Emory Healthcare (See Appendix A).

Chapter V: Discussion

Despite that novel immunosuppressive treatments have shown safety and efficacy to avoid graft rejection, accurate and reliable methods to understand CMV infection and manage risk groups are needed and are still a challenge. Our study developed the AUC method as an analytical tool for measuring Cytomegalovirus viral load to understand CMV dynamics on kidney transplant patients. First, we stratified groups based on CMV Donor/Recipient status (Donor (+)/Recipient (-): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk) to establish the differences among stratified groups and their AUC. Results showed a significant association between CMV high risk (Donor positive/Recipient negative) and higher magnitude and quantity, in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive). Second, we established the differences among CMV viral loads from the AUC of the immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5. Results showed that there was not a

significant difference among CMV AUC and the immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 used at Emory Healthcare. Establishing risk factors such as Donor/Recipient CMV status and immunosuppressive treatments' effect is vital for the management of Cytomegalovirus on kidney transplant patients. Identifying these risk factors, which predispose patients to an increased risk of developing CMV, through the application of AUC, will contribute to having successful transplantation outcomes, and support clinical strategies to contribute to public health solutions.

The results showed a significant association between CMV high risk (Donor positive/Recipient negative) and higher magnitude and quantity, in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive). Since there was not previous CMV immunity, because the recipients were negative, the Donor positive/Recipient negative group was more vulnerable.[19] Likewise, the immunosuppressive treatments can predispose kidney transplant patients to have CMV infection.[48] Using analytical tools to identify CMV high-risk groups will promote new strategies for CMV monitoring, testing and treatment. In our study, we found that CMV AUC post-transplant was significantly higher for the high risk group (Donor positive / Recipient negative), which confirms the crucial role that donor recipient match can play in heightening CMV infection risk.[4] Identifying the CMV high risk group (Donor positive/Recipient negative), which has higher magnitude and quantity in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive), will allow practitioners to utilize efficient allocation of resources on those patients that are more at risk, and/or less resources may be allocated to those with less risk.

Our results showed that there was not a significant difference in CMV AUC under the five immunosuppressive treatments used at Emory Healthcare: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5. While we did not see a significant decrease in AUC CMV among Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 groups, we also did not find a significant increase in AUC CMV among Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 groups. It has been demonstrated that high immunosuppressive treatment is associated with a high risk of CMV infection; Tacrolimus regimes are more likely to develop CMV disease compared with those patients on Cyclosporine treatment.[49] However, since Cyclosporine was not used in our study, we could not evaluate Cyclosporine, Tacrolimus 1.5 and the Belatacept cohorts and compare their CMV viral load. Belatacept has been demonstrated to be efficient and safe as an immunosuppressive treatment in transplantation.[25,27] Although Belatacept clinical trial evaluations have been focused mostly on assessing graft function and mortality, and comparing cardiovascular/metabolic risk,[50] CMV infection rates have been reported to be similar to the rates when calcineurin inhibitors treatments are used.[51] The different immunosuppressive treatments used at Emory Healthcare: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept

2.3, and Tacrolimus 1.5, might not be a risk factor for the occurrence of CMV at Emory Healthcare.

We observed that the high and moderate CMV risk were similarly distributed among Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 immunosuppressive treatments (Table 2. CMV Risk Status). The distribution of High and moderate CMV risk groups allows us to identify CMV risk status as a key factor rather than the effect of immunosuppressive treatments used at Emory Healthcare.

Further applications for AUC methodologies as a data capture tool could be implemented as part of Business Intelligence tools and be a real-time resource for the practitioners to do their own analysis and make prompt decisions. Having AUC as a data capture methodology incorporated on the clinic browser could assist physicians to have instantaneous CMV result analysis, providing better patient viral management and achieving the best treatment strategy. Additionally, AUC is a promising tool to explore not only other viruses related to transplantation, but also other areas such as sepsis and investigating the incidence of other viruses that are becoming public health concerns.

Our study had some limitations. Since there was not a homogenous distribution of the low risk patients among groups, it was not possible to make comparisons with the high and moderate risk groups to evaluate the impact of high-risk group (Donor (+)/Recipient (-)) among Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 immunosuppressive treatment groups. Further studies are needed to evaluate CMV group risk status across states to determine demographic differences and risk group distribution and help understand CMV dynamics in the U.S. The number of CMV tests collected from Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 was not consistent, which may have prevented showing the effect of the immunosuppressive treatments on the AUC CMV viral load. Our study had a small population, which limited the applicability of our results to other populations. Additional studies with larger sample size, more collection times, and the integration with other transplant centers could provide deeper analysis for the immunosuppressive treatments used at Emory Healthcare.

In summary, developing AUC and applying data capture as analytical tools can support clinical operations to monitor transplant patients focusing on the high-risk groups and having efficient resource allocation to contribute to make prompt and effective clinical decisions that will impact public health solutions and transplant outcomes.

Appendix A

Data Dictionary

The following data dictionary was an adaptation as part of the workflow methodology and software of research electronic data capture (REDCap) to monitor CMV for transplant patients at Emory Healthcare[38,39]

A	B	C	D	E
Variable / Field Name	Form Name	Section Header	Field Type	Field Label
study_id	demographics		text	Study ID
date_enrolled	demographics	Demographic Characteristics	text	Date subject signed consent
first_name	demographics		text	First Name
last_name	demographics		text	Last Name
address	demographics	Contact Information	notes	Street, City, State, ZIP
telephone_1	demographics		text	Phone number
telephone_2	demographics		text	Second phone number
email	demographics		text	E-mail
sex	demographics		dropdown	Gender
given_birth	demographics		dropdown	Has the subject given birth before?
num_children	demographics		text	How many times has the subject given birth?
ethnicity	demographics		radio	Ethnicity
race	demographics		checkbox	Race
dob	demographics		text	Date of birth
age	demographics		calc	Age (years)
height	demographics		text	Height (cm)
weight	demographics		text	Weight (kilograms)
bmi	demographics		calc	BMI
patient_document	demographics		file	Patient document
comorbidities	demographics		text	Any comorbid condition
diabetes	demographics		dropdown	Patient has a diagnosis of diabetes mellitus?
diabetes_type	demographics		dropdown	Type of Diabetes Mellitus
dialysis_initiation	demographics	Dialysis Information	text	Date of first outpatient dialysis treatment

access_type	demographics		dropdown	Type of vascular access
access_location	demographics		dropdown	Location of currently used vascular access
dialysis_unit_name	demographics		text	Name of dialysis unit
dialysis_unit_phone	demographics		text	Phone number
etiology_esrd	demographics		dropdown	Etiology of ESRD
subject_comments	demographics	General Comments	notes	Comments
date_visit_b	baseline_data	Baseline Measurements	text	Date of baseline visit
date_blood_b	baseline_data		text	Date blood was drawn
alb_b	baseline_data		text	Serum Albumin (g/dL)
prealb_b	baseline_data		text	Serum Prealbumin (mg/dL)
creat_b	baseline_data		text	Creatinine (mg/dL)
npcr_b	baseline_data		text	Normalized Protein Catabolic Rate (g/kg/d)
chol_b	baseline_data		text	Cholesterol (mg/dL)
plasma1_b_cmv	baseline_data		dropdown	Collected Plasma 1?
plasma2_b_cmv	baseline_data		dropdown	Collected Plasma 2?
plasma3_b_cmv	baseline_data		dropdown	Collected Plasma 3?
serum1_b_cmv	baseline_data		dropdown	Collected Serum 1?
serum2_b_cmv	baseline_data		dropdown	Collected Serum 2?
serum3_b_cmv	baseline_data		dropdown	Collected Serum 3?
sga_b	baseline_data		text	Subject Global Assessment (score = 1-7)
date_visit_1	month_1_data	Month 1	text	Date of Month 1 visit
alb_1	month_1_data		text	Serum Albumin (g/dL)
prealb_1	month_1_data		text	Serum Prealbumin (mg/dL)
creat_1	month_1_data		text	Creatinine (mg/dL)
npcr_1	month_1_data		text	Normalized Protein Catabolic Rate (g/kg/d)
chol_1	month_1_data		text	Cholesterol (mg/dL)
cmv_rec	month_1_data		text	
cmv_d	month_1_data		text	

F	G	H	I	J	K	L
Choices, Calculations, OR Slider Labels	Field Note	Text Validation Type OR Show Slider Number	Text Validation Min	Text Validation Max	Identifier	Branching Logic (Show field only if...)
	YYYY-MM-DD	date				
					y	
					y	
					y	
	Include Area Code	phone			y	
	Include Area Code	phone			y	
		email			y	
0, Female | 1, Male						
0, No | 1, Yes						[sex] = "0"
		integer	0			[sex] = "0" and [given_birth] = "1"
0, Hispanic or Latino | 1, NOT Hispanic or Latino | 2, Unknown / Not Reported						
0, American Indian/Alaska Native | 1, Asian | 2, Native Hawaiian or Other Pacific Islander | 3, Black or African American | 4, White|5 M ore than one race | 6, Unknown						
		date			y	
round(datediff([dob],'today','y'),0)						
		number	130	215		
		integer	35	200		
round(([weight]*10000)/(([height])^(2)),1)						

0, No | 1, Yes						
0, Type 1 insulin-dependent | 1, Type 2 insulin-dependent | 2, Type 2 non insulin-dependent						
		date				
0, Graft | 1, Fistula | 2, Catheter with maturing graft | 3, Catheter with maturing fistula						
0, Forearm | 1, Upper arm | 2, Internal jugular vein | 3, Subclavian vein | 4, Other | 5, Hereditary Nephritis | 6, Other						
	Include Area Code	phone				
0, Diabetes | 1, Hypertension | 2, Glomerulonephritis | 3, Polycystic Kidney Disease | 4, Interstitial Nephritis |						
		date				
		date				
		integer	3	5		
		number	10	40		
		number	0.5	20		
		number	0.5	2		
		number	100	300		
0, No | 1, Yes						
0, No | 1, Yes						
0, No | 1, Yes						
0, No | 1, Yes						
0, No | 1, Yes						

0, No | 1, Yes						
		number	0.9	7.1		
		date				
		number	3	5		
		number	10	40		
		number	0.5	20		
		number	0.5	2		
		number	100	300		

References

1. Schoolwerth AC, Engelgau MM, Rufo KH, et al. Chronic Kidney Disease: A Public Health Problem That Needs a Public Health Action Plan. *Prev Chronic Dis*. Apr 2006;3(2).
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. Oct 2011;11(10):2093-2109.
3. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2012 Annual Data Report: kidney. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. Jan 2014;14 Suppl 1:11-44.
4. Kotton CN, Kumar D, Caliendo AM, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. Aug 27 2013;96(4):333-360.
5. Patel R, Paya CV. Infections in solid-organ transplant recipients. *Clinical microbiology reviews*. Jan 1997;10(1):86-124.
6. Razonable RR. Epidemiology of cytomegalovirus disease in solid organ and hematopoietic stem cell transplant recipients. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Apr 15 2005;62(8 Suppl 1):S7-13.
7. van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jul 1 2001;33 Suppl 1:S32-37.
8. Razonable RR, Rivero A, Rodriguez A, et al. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *The Journal of infectious diseases*. Dec 1 2001;184(11):1461-1464.
9. Schafer P, Tenschert W, Cremaschi L, Schroter M, Zollner B, Laufs R. Area under the viraemia curve versus absolute viral load: utility for predicting symptomatic cytomegalovirus infections in kidney transplant patients. *J Med Virol*. Sep 2001;65(1):85-89.
10. CDC. National Center for Chronic Disease Prevention and Health Promotion Division of Diabetes Translation National Chronic Kidney Disease Fact Sheet, 2014. 2014; http://www.cdc.gov/diabetes/pubs/pdf/kidney_Factsheet.pdf, February 20, 2016.
11. Services USDoHaH. The Growing Burden of Kidney Disease. *Kidney Disease Statistics for the United States*. Bethesda, MD: Clearinghouse 2012:16.
12. United States Renal Data System. National Institute of Diabetes and Digestive and Kidney Disease (NIDDK); 2015.

https://http://www.usrds.org/2015/view/v1_01.aspx. Accessed July 20, 2016.
13. United States Renal Data System. National Institute of Diabetes and Digestive and Kidney Disease (NIDDK); 2010. https://http://www.usrds.org/atlas10.aspx. Accessed July 24,2016.
14. Office of Disease Prevention adn Health Promotion USGP. Chapter 2: Healthy People 2020. About People. Retrived February 20, 2016. http://www.usrds.org/2014/download/V2_Ch_2_HP2020_14.pdf, 2010-2014.
15. McClellan WMS, A.C.; Gehr,T. *Clincal Management of Chronic Kidney Disease*. First ed: Professional Communications, Inc; 2006.
16. Naumnik B, Malyszko J, Chyczewski L, Kovalchuk O, Malyszko J, Mysliwiec M. Comparison of serology assays and polymerase chain reaction for the monitoring of active cytomegalovirus infection in renal transplant recipients. *Transplant Proc*. Nov 2007;39(9):2748-2750.
17. Beam E, Razonable RR. Cytomegalovirus in solid organ transplantation: epidemiology, prevention, and treatment. *Curr Infect Dis Rep*. Dec 2012;14(6):633-641.
18. Mehta AL, K.; Walker, A. Rates of CMV at the Emory Transplant Center. ETC Quality Meetings: Emory University.
19. Razonable RR, Hayden RT. Clinical utility of viral load in management of cytomegalovirus infection after solid organ transplantation. *Clinical microbiology reviews*. Oct 2013;26(4):703-727.
20. Cukuranovic J, Ugrenovic S, Jovanovic I, Visnjic M, Stefanovic V. Viral infection in renal transplant recipients. *ScientificWorldJournal*. 2012;2012:820621.
21. Vicari-Christensen M, Repper S, Basile S, Young D. Tacrolimus: review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence. *Prog Transplant*. Sep 2009;19(3):277-284.
22. Magazine AM. Emory's Drs. Larsen and Pearson help develop the drug Belatacept. Atlanta Medicine Magazine; 2016.
23. Administration FUSFaD. FDA approves Nulojix for kidney transplant patients. 2011; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm259184.htm. Accessed July 22, 2016, 2016.
24. Larsen CP, Pearson TC, Adams AB, et al. Rational development of LEA29Y (belatacept), a high-affinity variant of CTLA4-Ig with potent immunosuppressive properties. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. Mar 2005;5(3):443-453.
25. Grannas G, Schrem H, Klempnauer J, Lehner F. Ten years experience with belatacept-based immunosuppression after kidney transplantation. *Journal of clinical medicine research*. Apr 2014;6(2):98-110.
26. Rostaing L, Vincenti F, Grinyo J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. *American journal of transplantation :*

official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. Nov 2013;13(11):2875-2883.
27. Larsen CP, Grinyo J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation*. Dec 27 2010;90(12):1528-1535.
28. Torres-Madriz G, Boucher HW. Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Sep 1 2008;47(5):702-711.
29. Steiner RW, Awdishu L. Steroids in kidney transplant patients. *Seminars in immunopathology*. Mar 2011;33(2):157-167.
30. Baxter JD. The effects of glucocorticoid therapy. *Hospital practice*. Sep 15 1992;27(9):111-114, 115-118, 123 passim.
31. Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. *Lancet*. Jun 10 2000;355(9220):2032-2036.
32. Bhatia J, Shah BV, Mehta AP, Deshmukh M, Sirsat RA, Rodrigues C. Comparing serology, antigenemia assay and polymerase chain reaction for the diagnosis of cytomegalovirus infection in renal transplant patients. *The Journal of the Association of Physicians of India*. Apr 2004;52:297-300.
33. Jordan CL, Taber DJ, Kyle MO, et al. Incidence, risk factors, and outcomes of opportunistic infections in pediatric renal transplant recipients. *Pediatr Transplant*. Nov 18 2015.
34. Harvala H, Stewart C, Muller K, et al. High risk of cytomegalovirus infection following solid organ transplantation despite prophylactic therapy. *Journal of medical virology*. May 2013;85(5):893-898.
35. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. May 2010;10(5):1228-1237.
36. Yao W, Hertel L, Wahl LM. Dynamics of recurrent viral infection. *Proceedings. Biological sciences / The Royal Society*. Sep 7 2006;273(1598):2193-2199.
37. Terasaki PI, Yuge J, Cecka JM, Gjertson DW. Cytomegalovirus antibody status and kidney transplantation. *Clinical transplants*. 1994:509-518.
38. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. Apr 2009;42(2):377-381.
39. Project REDCap. Training Resources - Data Dictionary using REDCap electronic data capture tools hosted at Emory University. 2016; Video Resources- Screenshot. Available at: http://project-redcap.org.

40. Healthcare E. Kidney Transplant Program - Quality Outcomes. http://www.emoryhealthcare.org/transplant-kidney/quality-indicators.html. Accessed December 30, 2015.
41. Mehta ALK. Initial Protocol Start Dates associated with the various Bela and Tac cohorts. In: A. G, ed2016.
42. Office USGP. Electronic Code of Federal Regulations. *Subchapter C - Adminstrative data standards and related requirements - Part 164-Security and Privacy* 2016; http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title45/45cfr164_main_02.tpl
43. Shostak J. De-Identification of Clinical Trials Data Demystified.
44. Alexandrov O. Trapezoide rule. In: ilustration.png Ctr, ed. https://upload.wikimedia.org/wikipedia/commons/b/b1/Composite_trapezoidal_rule_illustration.svg2007.
45. Buclin T. Area under the plasma drug concentration-time curve. 2009; http://sepia.unil.ch/pharmacology/index.php?id=66. Accessed July 21, 2016, 2016.
46. Herbers PE, D.; Woo,J. Ara under a Curve: Calculation and Visualization. Vol Paper DG12-2011: Cincinnati Children's Hospital Medical Center; 2011:1-12.
47. Shiang K-D. The SAS® Calculations of Areas Under the Curve (AUC) for Multiple Metaboki Readings. City of Hope National Medical Center:1-14.
48. Cordero E, Casasola C, Ecarma R, Danguilan R. Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors. *Transplantation proceedings*. Apr 2012;44(3):694-700.
49. Nafar M, Roshan A, Pour-Reza-Gholi F, et al. Prevalence and risk factors of recurrent cytomegalovirus infection in kidney transplant recipients. *Iranian journal of kidney diseases*. May 2014;8(3):231-235.
50. Vincenti F, Blancho G, Durrbach A, et al. Five-Year Safety and Efficacy of Belatacept in Renal Transplantation. *Journal of the American Society of Nephrology : JASN*. Sep 2010;21(9):1587-1596.
51. Becker BN, Becker YT, Leverson GE, Simmons WD, Sollinger HW, Pirsch JD. Reassessing the impact of cytomegalovirus infection in kidney and kidney-pancreas transplantation. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. May 2002;39(5):1088-1095.